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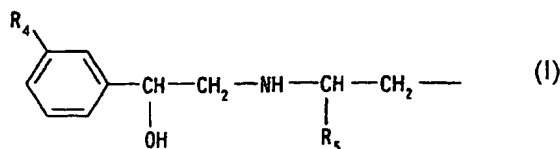
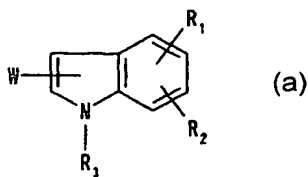
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(54) Title: PHARMACEUTICAL COMPOSITION



(57) Abstract: A pharmaceutical composition which comprises an insulin sensitizer in combination with a compound (a) of formula (I), wherein R<sub>1</sub> represents a lower alkyl group optionally substituted by hydroxyl group, etc., R<sub>2</sub> represents hydrogen atom, etc., R<sub>3</sub> represents hydrogen atom, etc., W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in formula (I), wherein R<sub>4</sub> represents a halogen atom, etc., R<sub>5</sub> represents a lower alkyl group, or a salt thereof, which is useful as an agent for preventing or treating diabetes.

## DESCRIPTION

## PHARMACEUTICAL COMPOSITION

## TECHNICAL FIELD

- 5       The present invention relates to a pharmaceutical composition which is useful as an agent for preventing or treating diabetes, etc., comprising an insulin sensitizer (insulin resistance-improving agent).

## 10 BACKGROUND ART

Examples of prior art references which describe a  $\beta 3$  adrenaline receptor agonist are shown below.

- 1) WO98/32753 describes that thiazole substituted benzenesulfonamides are  $\beta 3$  adrenergic receptor agonists.
- 15 2) Diabetes Frontier, Vol. 8, p.499 (1997) describes that when CL316243 ( $\beta 3$  adrenergic receptor agonist) and troglitazone were administered to obese rats, "CL316243 completely inhibited a weight increase in brown adipose tissues caused by troglitazone".
- 20 3) JP-A H5(1993)-148496 describes that 4-[2-(2-hydroxy-2-phenyl-ethylamino)ethoxy]phenylacetic acid and its precursors are  $\beta 3$  adrenergic receptor agonists.
- 4) WO96/16938 describes a novel indole derivative having a potent  $\beta 3$  adrenergic receptor stimulating activity.

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Development of excellent drugs which are sufficiently improved as medicines having an excellent diabetic treatment effect without apparent detection of side effects is desired.

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## DISCLOSURE OF INVENTION

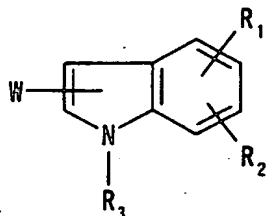
- As a result of various studies in use of an insulin sensitizer in combination with other drugs, the present inventors have found a novel combination that provides
- 35 unexpectedly excellent effects. Based on this finding, the present inventors have completed the present invention.

Namely, the present invention relates to

(1) a pharmaceutical composition which comprises an insulin sensitizer in combination with at least one member selected

5 from the group consisting of

1) a compound of the formula [I] :



wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

(a) a group of the formula :  $-Xa-Ra$

wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;

20 (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,

25 (c) a group of the formula :  $-O(CH_2)_r-Rc$

wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$

wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

30 (d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower

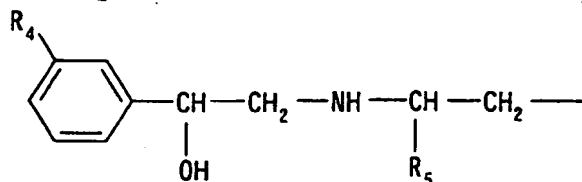
alkoxycarbonyl group,  $s$  is an integer of 1 to 4,

$R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above

- 5 (b) or (c), or combines with  $R_1$  to form the above methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxycarbonyl group,

$R_3$  represents hydrogen atom or a lower alkyl group,

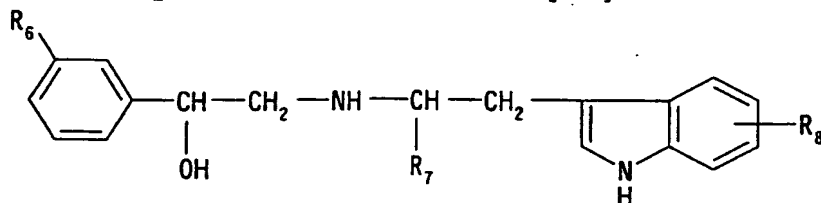
- 10 W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;

15

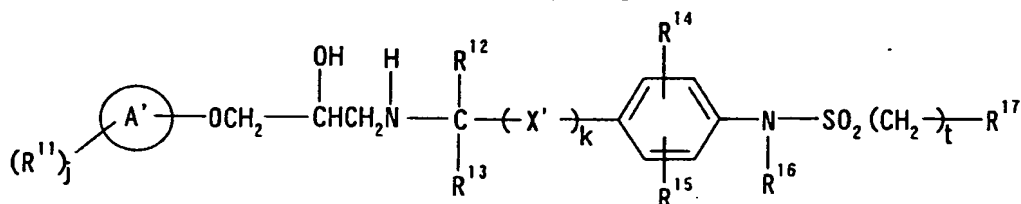
2) a compound of the formula [II] :



wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

20

3) a compound of the formula [III] :



- 25 wherein  $j$  represents an integer of 0 to 7,

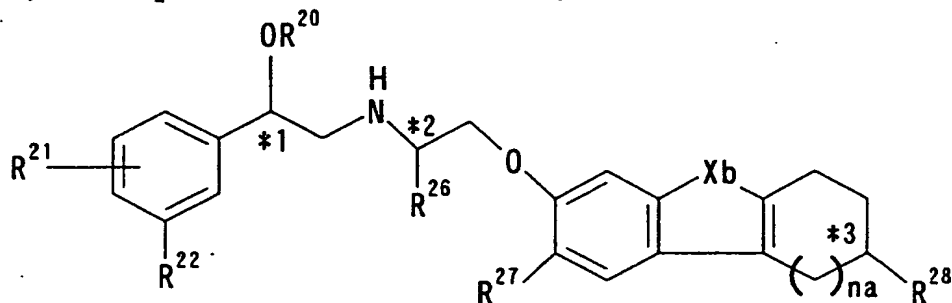
- k represents 0 or 1,  
t represents an integer of 0 to 3,  
ring A' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms  
5 selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and  
10 N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;  
R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>,  
15 NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;  
20 or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;  
R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;  
X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;  
25 R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;  
R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;  
R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub>,  
wherein R<sup>11</sup> and j have the same meanings as above;  
30 ring B' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms  
35 selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and

N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;

$R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$  alkyl substituted by hydroxy, halogen,  $CO_2H$ ,  $C_{1-6}$  alkoxy-carbonyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkoxy, or phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;

$R^{19}$  represents  $R^{18}$ ,  $NHR^{18}$  or  $NR^{18}$  wherein  $R^{18}$  has the same meaning as above, or a salt thereof;

4) a compound of the formula [V] :



wherein  $R^{20}$  represents hydrogen atom or methyl group,

$R^{21}$  represents hydrogen atom, halogen atom, hydroxy group,

benzyloxy group, amino group or hydroxymethyl group,

$R^{22}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{23}$ ,  $SO_2NR^{24}R^{24'}$  or nitro group,

$R^{23}$  represents hydrogen atom, methyl group,  $SO_2NR^{25}$ , formyl group or  $CONHR^{26'}$ ,

$R^{25}$  represents a lower alkyl group, benzyl group or  $NR^{24}R^{24'}$ ,  $R^{24}$  and  $R^{24'}$  are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

$R^{26'}$  represents hydrogen atom or a lower alkyl group,

$R^{26}$  represents hydrogen atom or a lower alkyl group,

na is 1 or 2,

Xb represents secondary nitrogen atom, O or S,

one of  $R^{27}$  or  $R^{28}$  is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 1,

$R^{28}$  is hydrogen atom, and  $R^{27}$  is hydrogen atom, amino group,

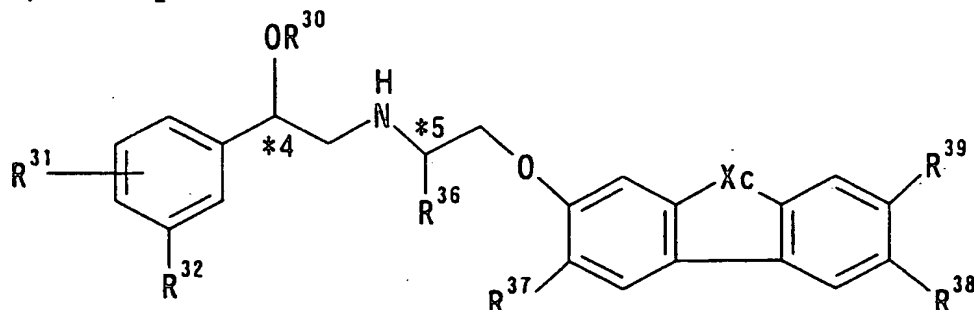
acetylamino group or hydroxy group, when na is 2,

\*1 represents an asymmetric carbon atom,

\*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof;

5 and

5) a compound of the formula [VI] :



wherein R<sup>30</sup> represents hydrogen atom or methyl group,

R<sup>21</sup> represents hydrogen atom, a halogen atom, hydroxy group,

10 benzyloxy group, amino group or hydroxymethyl group,

R<sup>32</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>33</sup>, SO<sub>2</sub>NR<sup>34</sup>R<sup>34'</sup> or nitro group,

R<sup>33</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>35</sup>, formyl group or CONHR<sup>36'</sup>,

15 R<sup>35</sup> represents a lower alkyl group, benzyl group or NR<sup>34</sup>R<sup>34'</sup>,

R<sup>34</sup> and R<sup>34'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

R<sup>36'</sup> represents hydrogen atom or a lower alkyl group,

R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

20 Xc represents secondary nitrogen atom, O, S or methylene group,

R<sup>39</sup> is hydrogen atom, one of R<sup>37</sup> or R<sup>38</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is secondary nitrogen atom, O or

25 S,

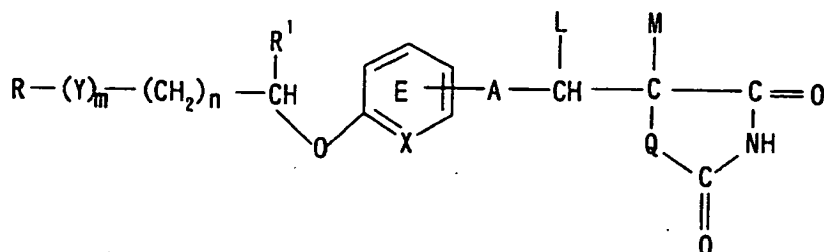
R<sup>37</sup> and R<sup>38</sup> are both hydrogen atom, and R<sup>39</sup> is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is methylene group,

\*4 represents an asymmetric carbon atom,

30 \*5 represents an asymmetric carbon atom when R<sup>36</sup> is a lower

alkyl group, or a salt thereof;

(2) a pharmaceutical composition according to the above (1), wherein the insulin sensitizer is a compound of the formula [IV] :



wherein R represents a hydrocarbon group or a heterocyclic group, each of which may be substituted; Y represents a group of the formula : -CO-, -CH(OH)- or -NR<sup>3</sup>- wherein R<sup>3</sup> represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents O or S; R<sup>1</sup> represents hydrogen atom or an alkyl group; ring E may have further 1 to 4 substituents, which may form a ring in combination with R<sup>1</sup>; L and M respectively represent hydrogen atom or may be combined with each other to form a chemical bond, or a salt thereof;

(3) a pharmaceutical composition according to the above (2),  
wherein the compound of the formula [IV] or a salt thereof  
20 is pioglitazone or its salt;

(4) a pharmaceutical composition according to the above (2), wherein the compound of the formula [IV] or a salt thereof is rosiglitazone or its salt;

25 (5) a pharmaceutical composition according to the above (1),  
which comprises pioglitazone or its hydrochloride in  
combination with 2-[3-(7-carboxymethoxyindol-3-yl)-

(2R)-2-propylamino]-(1R)-1-(3-chlorophenyl)ethanol;  
(6) a pharmaceutical composition according to the above (1),  
which comprises rosiglitazone or its maleate in combination  
30 with 2-[3-(7-carboxymethoxyindol-3-yl)-(2R)-2-  
propylamino]-(1R)-1-(3-chlorophenyl)ethanol;



(7) a pharmaceutical composition according to the above (1), which is for preventing or treating diabetes;

(8) a pharmaceutical composition according to the above (7), wherein the diabetes is noninsulin-dependent diabetes

5 mellitus;

(9) a pharmaceutical composition according to the above (1), which is for preventing or treating impaired glucose tolerance, hyperlipidemia, hyperinsulinemia, obesity, hyperphagia, hypertension, cardiovascular diseases,

10 polycystic ovary syndrome, gestational diabetes, pancreatitis, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis, inflammatory bowel diseases, syndrome X, visceral fat obesity syndrome or diabetic complications;

15 (10) a pharmaceutical composition according to the above (9), wherein the diabetic complications are retinopathy, nephropathy, neuropathy, macroangiopathy, diabetic hyperosmolar coma, infectious disease, diabetic osteoporosis, diabetic gangrene, xerostomia, lowered sense  
20 of hearing, myocardial infarction, angina pectoris, cerebrovascular disease or peripheral circulatory disturbance;

(11) a pharmaceutical composition for inhibiting body weight increase after stopping a smoking habit, which  
25 comprises at least one member selected from the group consisting of

1) a compound of the formula [I] or a salt thereof;

2) a compound of the formula [II] or a salt thereof;

3) a compound of the formula [III] or a salt thereof;

30 4) a compound of the formula [V] or a salt thereof; and

5) a compound of the formula [VI] or a salt thereof;

(12) a pharmaceutical composition for inhibiting body weight increase after stopping alimentary therapy, which comprises at least one member selected from the group

35 consisting of

1) a compound of the formula [I] or a salt thereof;

- 2) a compound of the formula [II] or a salt thereof;
  - 3) a compound of the formula [III] or a salt thereof;
  - 4) a compound of the formula [V] or a salt thereof; and
  - 5) a compound of the formula [VI] or a salt thereof;
- 5 (13) a method for preventing or treating diabetes in a mammal in need thereof, which comprises administering to said mammal an effective amount of an insulin sensitizer in combination with at least one member selected from the group consisting of
- 10 1) a compound of the formula [I] or a salt thereof;
  - 2) a compound of the formula [II] or a salt thereof;
  - 3) a compound of the formula [III] or a salt thereof;
  - 4) a compound of the formula [V] or a salt thereof; and
  - 5) a compound of the formula [VI] or a salt thereof;
- 15 (14) a method for preventing or treating impaired glucose tolerance, hyperlipidemia, hyperinsulinemia, obesity, hyperphagia, hypertension, cardiovascular diseases, polycystic ovary syndrome, gestational diabetes, pancreatitis, glomerulonephritis, glomerular sclerosis,
- 20 hypertensive nephrosclerosis, inflammatory bowel diseases, syndrome X, visceral fat obesity syndrome or diabetic complications, in a mammal in need thereof, which comprises administering to said mammal an effective amount of an insulin sensitizer in combination with at least one member
- 25 selected from the group consisting of
- 1) a compound of the formula [I] or a salt thereof;
  - 2) a compound of the formula [II] or a salt thereof;
  - 3) a compound of the formula [III] or a salt thereof;
  - 4) a compound of the formula [V] or a salt thereof; and
  - 30 5) a compound of the formula [VI] or a salt thereof;
- (15) a method according to the above (14), wherein the diabetic complications are retinopathy, nephropathy, neuropathy, macroangiopathy, diabetic hyperosmolar coma, infectious disease, diabetic osteoporosis, diabetic
- 35 gangrene, xerostomia, lowered sense of hearing, myocardial infarction, angina pectoris, cerebrovascular disease or

peripheral circulatory disturbance;

(16) a method for inhibiting body weight increase after stopping a smoking habit in human in need thereof, which comprises administering to said human an effective amount  
5 of at least one member selected from the group consisting of

1) a compound of the formula [I] or a salt thereof;

2) a compound of the formula [II] or a salt thereof;

3) a compound of the formula [III] or a salt thereof;

10 4) a compound of the formula [V] or a salt thereof; and

5) a compound of the formula [VI] or a salt thereof;

(17) a method for inhibiting body weight increase after stopping alimentary therapy in human in need thereof, which comprises administering to said human an effective amount  
15 of at least one member selected from the group consisting of

1) a compound of the formula [I] or a salt thereof;

2) a compound of the formula [II] or a salt thereof;

3) a compound of the formula [III] or a salt thereof;

20 4) a compound of the formula [V] or a salt thereof; and

5) a compound of the formula [VI] or a salt thereof;

(18) use of an insulin sensitizer for the manufacture of a pharmaceutical preparation for treating diabetes, which is used in combination with at least one member selected  
25 from the group consisting of

1) a compound of the formula [I] or a salt thereof;

2) a compound of the formula [II] or a salt thereof;

3) a compound of the formula [III] or a salt thereof;

4) a compound of the formula [V] or a salt thereof; and

30 5) a compound of the formula [VI] or a salt thereof;

(19) use of at least one member selected from the group consisting of

1) a compound of the formula [I] or a salt thereof;

2) a compound of the formula [II] or a salt thereof;

35 3) a compound of the formula [III] or a salt thereof;

4) a compound of the formula [V] or a salt thereof; and

- 5) a compound of the formula [VI] or a salt thereof,  
for the manufacture of a pharmaceutical preparation for  
treating diabetes, which is used in combination with an  
insulin sensitizer;
- 5 (20) use of an insulin sensitizer for the manufacture of  
a pharmaceutical preparation for treating impaired glucose  
tolerance, hyperlipidemia, hyperinsulinemia, obesity,  
hyperphagia, hypertension, cardiovascular diseases,  
polycystic ovary syndrome, gestational diabetes,  
10 pancreatitis, glomerulonephritis, glomerular sclerosis,  
hypertensive nephrosclerosis, inflammatory bowel diseases,  
syndrome X, visceral fat obesity syndrome or diabetic  
complications, which is used in combination with at least  
one member selected from the group consisting of
- 15 1) a compound of the formula [I] or a salt thereof;  
2) a compound of the formula [II] or a salt thereof;  
3) a compound of the formula [III] or a salt thereof;  
4) a compound of the formula [V] or a salt thereof; and  
5) a compound of the formula [VI] or a salt thereof;
- 20 (21) use of at least one member selected from the group  
consisting of
- 1) a compound of the formula [I] or a salt thereof;  
2) a compound of the formula [II] or a salt thereof;  
3) a compound of the formula [III] or a salt thereof;  
25 4) a compound of the formula [V] or a salt thereof; and  
5) a compound of the formula [VI] or a salt thereof,  
for the manufacture of a pharmaceutical preparation for  
treating impaired glucose tolerance, hyperlipidemia,  
hyperinsulinemia, obesity, hyperphagia, hypertension,  
30 cardiovascular diseases, polycystic ovary syndrome,  
gestational diabetes, pancreatitis, glomerulonephritis,  
glomerular sclerosis, hypertensive nephrosclerosis,  
inflammatory bowel diseases, syndrome X, visceral fat  
obesity syndrome or diabetic complications;
- 35 which is used in combination with an insulin sensitizer;  
(22) use according to the above (20) or (21), wherein the

diabetic complications are retinopathy, nephropathy, neuropathy, macroangiopathy, diabetic hyperosmolar coma, infectious disease, diabetic osteoporosis, diabetic gangrene, xerostomia, lowered sense of hearing, myocardial infarction, angina pectoris, cerebrovascular disease or peripheral circulatory disturbance;

(23) use of at least one member selected from the group consisting of

- 1) a compound of the formula [I] or a salt thereof;
  - 2) a compound of the formula [II] or a salt thereof;
  - 3) a compound of the formula [III] or a salt thereof;
  - 4) a compound of the formula [V] or a salt thereof; and
  - 5) a compound of the formula [VI] or a salt thereof,
- for the manufacture of a pharmaceutical preparation for inhibiting body weight increase after stopping a smoking habit;

(24) use of at least one member selected from the group consisting of

- 1) a compound of the formula [I] or a salt thereof;
  - 2) a compound of the formula [II] or a salt thereof;
  - 3) a compound of the formula [III] or a salt thereof;
  - 4) a compound of the formula [V] or a salt thereof; and
  - 5) a compound of the formula [VI] or a salt thereof,
- for the manufacture of a pharmaceutical preparation for inhibiting body weight increase after stopping alimentary therapy.

The insulin sensitizer used in the present invention means any and all drugs that restore the impaired insulin receptor function and improve insulin resistance. Specific examples of the insulin sensitizer include compounds having thiazolidinedione or oxazolidinedione skeletons, preferably the above-mentioned compound of the formula (IV) or a salt thereof.

Referring to the formula (IV), examples of the

hydrocarbon group in the hydrocarbon group that may be substituted for R include aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic-aliphatic hydrocarbon groups, and aromatic hydrocarbon groups. The number of carbon atoms constituting such hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon group is preferably a  $C_{1-8}$  aliphatic hydrocarbon group. Examples of the aliphatic hydrocarbon group includes saturated  $C_{1-8}$  aliphatic hydrocarbon groups (e.g. alkyl groups, etc.) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl, and octyl; and unsaturated  $C_{2-8}$  aliphatic hydrocarbon groups (e.g. alkenyl groups, alkadienyl groups, alkynyl groups, alkadiynyl groups, etc.) such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptyne, and 1-octynyl.

The alicyclic hydrocarbon group is preferably a  $C_{3-7}$  alicyclic hydrocarbon group. Examples of the alicyclic hydrocarbon group include saturated  $C_{3-7}$  alicyclic hydrocarbon groups (e.g. cycloalkyl groups, etc.) such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. and unsaturated  $C_{3-7}$  alicyclic hydrocarbon groups (e.g. cycloalkenyl groups, cycloalkadienyl groups, etc.) such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, and 2,4-cycloheptadienyl.

The alicyclic-aliphatic hydrocarbon group is a group consisting of the above-described alicyclic hydrocarbon group and aliphatic hydrocarbon group (e.g. cycloalkyl-alkyl groups, cycloalkenyl-alkyl groups, etc.) and is preferably a C<sub>4-9</sub> alicyclic-aliphatic hydrocarbon group.

Examples of the alicyclic-aliphatic hydrocarbon group include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl, cycloheptylethyl, etc.

The aromatic-aliphatic hydrocarbon group is preferably a C<sub>7-13</sub> aromatic-aliphatic hydrocarbon group (e.g. aralkyl groups, etc.). Examples of the aromatic-aliphatic hydrocarbon group include C<sub>7-9</sub> phenylalkyl such as benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl; C<sub>11-13</sub> naphthylalkyl such as  $\alpha$ -naphthylmethyl,  $\alpha$ -naphthylethyl,  $\beta$ -naphthylmethyl, and  $\beta$ -naphthylethyl.

The aromatic hydrocarbon group is preferably a C<sub>6-14</sub> aromatic hydrocarbon group (e.g. aryl groups, etc.). Examples of the aromatic hydrocarbon group include phenyl and naphthyl ( $\alpha$ -naphthyl,  $\beta$ -naphthyl).

Referring to the formula (IV), examples of the heterocyclic group in the heterocyclic group that may be substituted for R is a 5- to 7-membered heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur, and nitrogen in addition to carbon as ring members or a condensed ring group. Examples of the condensed ring include one consisting of such 5- to 7-membered heterocyclic group with a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring, or a 5-membered ring containing one sulfur atom.

Examples of the heterocyclic group include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-

pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl, benzopyranyl and dihydrobenzopyranyl. The heterocyclic group is preferably pyridyl, oxazolyl or thiazolyl group.

Referring to the formula (IV), the hydrocarbon group and heterocyclic group for R may respectively have 1 to 5, preferably 1 to 3 substituents at substitutable positions.

Such substituents include for example aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen, nitro, amino groups that may be substituted, acyl groups that may be substituted, hydroxy groups that may be substituted, thiol groups that may be substituted, carboxyl groups that may be esterified, amidino, carbamoyl, sulfamoyl, sulfo, cyano, azido, and nitroso.

Examples of the aliphatic hydrocarbon group include straight-chain or branched aliphatic hydrocarbon groups having 1 to 15 carbon atoms, such as alkyl groups, alkenyl groups, and alkynyl groups.

The preferred alkyl group is a C<sub>1-10</sub> alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl, and decyl.

The preferred alkenyl group is a C<sub>2-10</sub> alkenyl group.



such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl,  
5 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, and 5-hexenyl.

The preferred alkynyl group is a  $C_{2-10}$  alkynyl group, such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl,  
10 and 5-hexynyl.

Examples of the alicyclic hydrocarbon group includes saturated or unsaturated alicyclic hydrocarbon groups having 3 to 12 carbon atoms, such as cycloalkyl groups, cycloalkenyl groups, and cycloalkadienyl groups.

The preferred cycloalkyl group is a  $C_{3-10}$  cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl,  
15 bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, and bicyclo[4.3.1]decyl.

The preferred cycloalkenyl group is a  $C_{3-10}$  cycloalkenyl group, such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, and 3-cyclohexen-1-yl.  
25

The preferred cycloalkadienyl group is a  $C_{4-10}$  cycloalkadienyl group, such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, and 2,5-cyclohexadien-1-yl.

The preferred aryl group is a  $C_{6-14}$  aryl group, such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl, and acenaphthylenyl.  
30

The preferred aromatic heterocyclic group includes monocyclic aromatic heterocyclic groups, such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-  
35

thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl; and condensed aromatic heterocyclic groups, such as

5 benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl,

10 purinyl, pteridinyl, carbazolyl,  $\alpha$ -carbolinyl,  $\beta$ -carbolinyl,  $\gamma$ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl,

15 imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, and 1,2,4-triazolo[4,3-b]pyridazinyl.

The preferred non-aromatic heterocyclic group

20 includes oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino, and thiomorpholino.

25 Examples of the halogen include fluorine, chlorine, bromine, and iodine.

Referring to the amino group that may be substituted, examples of the substituted amino group include N-mono-substituted amino groups and N,N-di-substituted amino

30 groups. Examples of the substituted amino group include amino groups having one or two substituents selected from the group consisting of C<sub>1-10</sub> alkyl groups, C<sub>2-10</sub> alkenyl groups, C<sub>2-10</sub> alkynyl groups, C<sub>3-10</sub> cycloalkyl groups, aromatic groups (e.g., phenyl), heterocyclic groups, or

35 C<sub>1-10</sub> acyl groups (e.g., C<sub>1-10</sub> alkanoyl groups, benzoyl, nicotinoyl) (e.g. methylamino, dimethylamino, ethylamino,

diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino, benzoylamino, nicotinoylamino, etc.).

5        Examples of the acyl group in the acyl groups that may be substituted include  $C_{1-13}$  acyl groups, for example,  $C_{1-10}$  alkanoyl groups,  $C_{3-10}$  alkenoyl groups,  $C_{4-10}$  cycloalkanoyl groups,  $C_{4-10}$  cycloalkenoyl groups,  $C_{6-12}$  aromatic carbonyl groups.

10       Preferred examples of the  $C_{1-10}$  alkanoyl groups include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, and octanoyl.

Preferred examples of the  $C_{3-10}$  alkenoyl groups include acryloyl, methacryloyl, crotonoyl, and isocrotonoyl.

15       Preferred examples of the  $C_{4-10}$  cycloalkanoyl groups include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, and cycloheptanecarbonyl.

Preferred examples of the  $C_{4-10}$  cycloalkenoyl groups include 2-cyclohexenecarbonyl.

20       Preferred examples of the  $C_{6-12}$  aromatic carbonyl groups include benzoyl, naphthoyl, and nicotinoyl.

Examples of the substituents in the substituted acyl groups include  $C_{1-3}$  alkyl groups,  $C_{1-3}$  alkoxy groups, halogen (e.g. chlorine, fluorine, bromine, etc.), nitro, hydroxy,

25       and amino.

Referring to the hydroxy group that may be substituted, examples of the substituted hydroxy includes alkoxy groups, cycloalkyloxy groups, alkenyloxy groups, cycloalkenyloxy groups, aralkyloxy groups, acyloxy groups, and aryloxy groups.

30       The preferred alkoxy group includes  $C_{1-10}$  alkoxy groups, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, and nonyloxy.

The preferred cycloalkyloxy group includes C<sub>3-10</sub> cycloalkyloxy groups, such as cyclobutoxy, cyclopentyloxy, and cyclohexyloxy.

5 The preferred alkenyloxy group includes C<sub>2-10</sub> alkenyloxy groups, such as allyloxy, crotyloxy, 2-pentyloxy, and 3-hexenyloxy.

The preferred cycloalkenyloxy group includes C<sub>3-10</sub> cycloalkenyloxy groups, such as 2-cyclopentyloxy, and 2-cyclohexenyloxy.

10 The preferred aralkyloxy group includes C<sub>7-10</sub> aralkyloxy groups, such as phenyl-C<sub>1-4</sub> alkyloxy (e.g. benzyloxy, phenethyloxy, etc.).

The preferred acyloxy group includes C<sub>2-13</sub> acyloxy groups, more preferably C<sub>2-4</sub> alkanoyloxy groups (e.g. 15 acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.).

The preferred aryloxy group includes C<sub>6-14</sub> aryloxy groups, such as phenoxy, and naphthyloxy. This aryloxy group may have 1 or 2 substituents. Examples of the 20 substituents include halogen (e.g. chlorine, fluorine, bromine, etc.). Examples of the substituted aryloxy group includes 4-chlorophenoxy.

Referring to the thiol group that may be substituted, examples of the substituted thiol group include alkylthio 25 groups, cycloalkylthio groups, alkenylthio groups, cycloalkenylthio groups, aralkylthio groups, acylthio groups, and arylthio groups.

The preferred alkylthio group includes C<sub>1-10</sub> alkylthio groups, such as methylthio, ethylthio, propylthio, 30 isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, and nonylthio.

The preferred cycloalkylthio group includes C<sub>3-10</sub> cycloalkylthio groups such as cyclobutylthio, 35 cyclopentylthio, and cyclohexylthio.

The preferred alkenylthio group includes C<sub>2-10</sub>

alkenylthio groups, such as allylthio, crotylthio, 2-pentenylthio, and 3-hexenylthio.

The preferred cycloalkenylthio group includes C<sub>3-10</sub> cycloalkenylthio groups such as 2-cyclopentenylthio, and  
5 2-cyclohexenylthio.

The preferred aralkylthio group includes C<sub>7-10</sub> aralkylthio groups, such as phenyl-C<sub>1-4</sub> alkylthio (e.g. benzylthio, phenethylthio, etc.).

The acylthio group is preferably a C<sub>2-13</sub> acylthio group,  
10 more preferably a C<sub>2-4</sub> alkanoylthio group (e.g. acetylthio, propionylthio, butyrylthio, isobutyrylthio, etc.).

The preferred arylthio group includes C<sub>6-14</sub> arylthio groups, such as phenylthio, and naphthylthio. This arylthio group may have 1 or 2 substituents. Examples of  
15 the substituents include halogen (e.g. chlorine, fluorine, bromine, etc.). Examples of the substituted arylthio group includes 4-chlorophenylthio.

The carboxyl group that may be esterified includes  
20 alkoxycarbonyl groups, aralkyloxycarbonyl groups, and aryloxycarbonyl groups.

The preferred alkoxycarbonyl group includes C<sub>2-5</sub> alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl.

25 The preferred aralkyloxycarbonyl group includes C<sub>8-10</sub> aralkyloxycarbonyl groups, such as benzyloxycarbonyl.

The preferred aryloxycarbonyl group includes C<sub>7-15</sub> aryloxycarbonyl groups, such as phenoxycarbonyl, and p-tolyloxycarbonyl.

30 The preferred substituent on the hydrocarbon group or heterocyclic group for R includes C<sub>1-10</sub> alkyl groups, aromatic heterocyclic groups, and C<sub>6-14</sub> aryl groups. Further preferred is C<sub>1-3</sub> alkyl, furyl, thienyl, phenyl, or naphthyl.

35

Referring to the formula (IV), when the substituent

on the hydrocarbon group or heterocyclic group for R is an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group, or a non-aromatic heterocyclic group, this substituent may further have one or more, preferably 1 to 3 suitable substituents. Examples of such substituents include C<sub>1-6</sub> alkyl groups, C<sub>2-6</sub> alkenyl groups, C<sub>2-6</sub> alkynyl groups, C<sub>3-7</sub> cycloalkyl groups, C<sub>6-14</sub> aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl, thiazolyl, etc.), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino, piperazino, etc.), C<sub>7-9</sub> aralkyl groups, amino, N-mono-C<sub>1-4</sub> alkylamino groups, N,N-di-C<sub>1-4</sub> alkylamino groups, C<sub>2-8</sub> acylamino groups (e.g. acetylamino, propionylamino, benzoylamino, etc.), amidino, C<sub>2-8</sub> acyl groups (e.g. C<sub>2-8</sub> alkanoyl groups, etc.), carbamoyl, N-mono-C<sub>1-4</sub> alkylcarbamoyl groups, N,N-di-C<sub>1-4</sub> alkylcarbamoyl groups, sulfamoyl, N-mono-C<sub>1-4</sub> alkylsulfamoyl groups, N,N-di-C<sub>1-4</sub> alkylsulfamoyl groups, carboxyl, C<sub>2-8</sub> alkoxy carbonyl groups, hydroxy, C<sub>1-4</sub> alkoxy groups, C<sub>2-5</sub> alkenyloxy groups, C<sub>3-7</sub> cycloalkyloxy groups, C<sub>7-9</sub> aralkyloxy groups, C<sub>6-14</sub> aryloxy groups, mercapto, C<sub>1-4</sub> alkylthio groups, C<sub>7-9</sub> aralkylthio groups, C<sub>6-14</sub> arylthio groups, sulfo, cyano, azido, nitro, nitroso, and halogen.

Referring to the formula (IV), R is preferably a heterocyclic group that may be substituted. More preferably, R is pyridyl, oxazolyl, or thiazolyl group, which may have 1 to 3 substituents selected from the group consisting of C<sub>1-3</sub> alkyl, furyl, thienyl, phenyl, and naphthyl.

Referring to the formula (IV), Y represents -CO-, -CH(OH)- or -NR<sup>3</sup>- wherein R<sup>3</sup> represents an alkyl group that may be substituted. Preferred is -CH(OH)- or -NR<sup>3</sup>-. Examples of an alkyl group in the alkyl group that may be substituted for R<sup>3</sup>, include C<sub>1-4</sub> alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, and

t.-butyl. Examples of the substituent include halogen (e.g. fluorine, chlorine, bromine, iodine),  $C_{1-4}$  alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, etc.), hydroxy, nitro, and  $C_{1-4}$  acyl groups (e.g. formyl, acetyl, propionyl, etc.).

The symbol m represents 0 or 1, and is preferably 0.

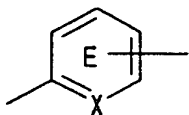
The symbol n represents 0, 1 or 2, and is preferably 0 or 1.

X represents CH or N, and is preferably CH.

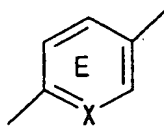
Referring to the formula (IV), A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms. This aliphatic hydrocarbon group may be straight-chain or branched and may further be saturated or unsaturated. Thus, for example,  $-CH_2-$ ,  $-CH(CH_3)-$ ,  $-(CH_2)_2-$ ,  $-CH(C_2H_5)-$ ,  $-(CH_2)_3-$ ,  $-(CH_2)_4-$ ,  $-(CH_2)_5-$ ,  $-(CH_2)_6-$ ,  $-(CH_2)_7-$ , etc. can be mentioned for the saturated bivalent aliphatic hydrocarbon group, while  $-CH=CH-$ ,  $-C(CH_3)=CH-$ ,  $-CH=CH-CH_2-$ ,  $-C(C_2H_5)=CH-$ ,  $-CH_2-CH=CH-CH_2-$ ,  $-CH_2-CH_2-CH=CH-CH_2-$ ,  $-CH=CH-CH=CH-CH_2-$ ,  $-CH=CH-CH=CH-CH=CH-CH_2-$ , etc. can be mentioned for the unsaturated bivalent aliphatic hydrocarbon group. A preferably represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 4 carbon atoms, which is preferably a saturated group. More preferably, A represents a chemical bond or  $-(CH_2)_2-$ .

The alkyl group for  $R^1$  includes the similar one to the alkyl group for the above-described  $R^3$ .  $R^1$  is preferably hydrogen atom.

Referring to the formula (IV), the partial structural formula:



is preferably  
the formula :

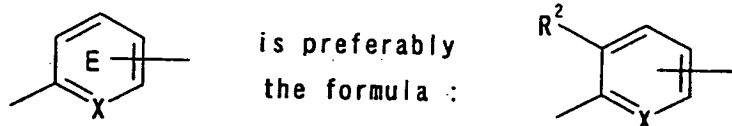


wherein each symbol has the same meanings as described above.

Furthermore, ring E may optionally have further 1 to

4 substituents at substitutable positions. Examples of such substituents include an alkyl group, a hydroxy group that may be substituted, halogen, an acyl group that may be substituted, nitro, and an amino group that may be substituted. These substituents are similar to those on the hydrocarbon group and heterocyclic group for the above-described R.

Ring E, namely the partial structural formula:



wherein  $R^2$  represents hydrogen atom, an alkyl group, a hydroxy group that may be substituted, halogen, an acyl group that may be substituted, nitro, or an amino group that may be substituted.

The alkyl group, hydroxy group that may be substituted, halogen, acyl group that may be substituted, and amino group that may be substituted, for  $R^2$ , are similar to those on the hydrocarbon group or heterocyclic group for the above-described R.  $R^2$  is preferably hydrogen atom, a hydroxy group that may be substituted, or halogen.  $R^2$  is more preferably hydrogen atom, or a hydroxy group that may be substituted.  $R^2$  is especially preferably hydrogen atom, or a  $C_{1-4}$  alkoxy group.

Referring to the formula (IV), L and M respectively represent hydrogen atom or may be combined with each other to form a chemical bond, and preferably they are hydrogen atom.

The compound in which L and M are combined with each other to form a chemical bond, may exist as (E)- and (Z)-isomers, owing to the double bond at 5-position of the azolidinedione ring.

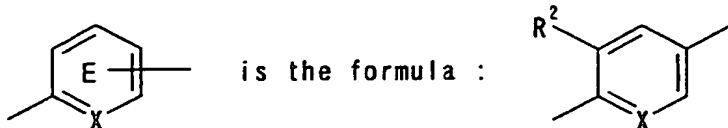
The compound in which L and M respectively represent hydrogen atom, may exist as optical isomers, i.e. (R)- and



(S)-forms, with respect to the asymmetric carbon at 5-position of the azolidinedione ring. This compound includes these optically active compounds, i.e. (R)- and (S)-forms, as well as the racemic form.

5

The preferred compound of the formula (IV) includes the compound in which R represents pyridyl, oxazolyl, or thiazolyl group, each of which may have 1 to 3 substituents selected from the group consisting of C<sub>1-3</sub> alkyl, furyl, thienyl, phenyl, and naphthyl; m is 0; n is 0 or 1; X represents CH; A represents a chemical bond or -(CH<sub>2</sub>)<sub>2</sub>-; R<sup>1</sup> represents hydrogen; ring E, namely the partial structural formula:



wherein R<sup>2</sup> is hydrogen or a C<sub>1-4</sub> alkoxy group; and L and M represent hydrogen atom.

Examples of the preferred compound of the formula (IV) includes

- 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone);
- 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone);
- 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: rosiglitazone);
- 5-[3-[4-(5-methyl-2-phenyl-4-thiazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione;
- 5-[4-(6-methoxy-1-H-benzimidazol-2-ylmethoxy)benzyl]-2,4-thiazolidinedione; and
- 5-[4-(6-methoxy-1-methylbenzimidazol-2-ylmethoxy)benzyl]-2,4-thiazolidinedione.

A salt of a compound represented by the formula (IV) is preferably a pharmacologically acceptable salt, which

includes salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

5 The preferred salt with an inorganic base includes salts with alkali metal such as sodium, potassium, etc.; alkaline earth metal such as calcium, magnesium, etc.; aluminum; ammonium etc.

10 The preferred salt with an organic base includes salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

The preferred salt with an inorganic acid includes salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

15 The preferred salt with an organic acid includes salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

20 The preferred salt with a basic amino acid includes salts with arginine, lysine, ornithine, etc. The preferred salt with an acidic amino acid includes salts with aspartic acid, glutamic acid, etc.

25 A compound represented by the formula (IV) or salt thereof is preferably pioglitazone, troglitazone, rosiglitazone or their salts; more preferably pioglitazone or its hydrochloride, troglitazone, rosiglitazone or its maleate; especially preferably pioglitazone  
30 hydrochloride.

A compound represented by the formula (IV) or salt thereof can be produced in accordance with methods described in JP-A S55(1980)-22636 (EP-A-8203), JP-A

35 S60(1985)-208980 (EP-A-155845), JP-A S61(1986)-286376 (EP-A-208420), JP-A S61(1986)-85372 (EP-A-177353), JP-A

S61(1986)-267580 (EP-A-193256), JP-A H5(1993)-86057 (WO-A-92/18501), JP-A H7(1995)-82269 (EP-A-605228), JP-A H7(1995)-101945 (EP-A-612743), EP-A-643050, EP-A-710659, USP 5002953, JP-A H9(1997)-295970, etc., or methods

5 analogous thereto.

Examples of the insulin sensitizer employed in the present invention include, in addition to the above-described compounds,

(±)-4-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]isoxazolidin-3,5-dione (JTT-501) or its salt;

5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its salt (preferably sodium salt);

15 5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its salt (preferably sodium salt);

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768) or its salt;

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637) or its salt;

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711) or its salt;

25 5-[[6-(2-fluorobenzyloxy)-2-naphthyl]methyl]-2,4-thiazolidinedione (MCC-555) or its salt;

(±)-[5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxy-N-[[4-(trifluoromethyl)phenyl]methyl]benzamido (AHG-255) or its salt;

30 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoic acid (LGD1069) or its salt;

6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic acid

35 (LGD100268) or its salt;

1,4-bis[4-[(3,5-dioxo-1,2,4-oxadiazolidin-2-

yl)methyl]phenoxy]-2-butene (YM-440) or its salt;  
R-119702; dexlipotam; GI-262570; INS-1; AR-H-0329242;  
CLX-0901; FK-614; KRP-297; CRE-16336; NN-2344; BM-13-1258;  
S-15261; KB-R-7785; DN-108; DRF-2725; GW-2570; GW-2433;  
5 MXC-3255; L-746449; L-767827; L-783281; GW-409544; CS-011;  
etc.

Salts of these compounds include those similar to the  
salt of a compound of the formula (IV) mentioned above.

10 An insulin sensitizer is preferably pioglitazone or  
its hydrochloride, troglitazone, rosiglitazone or its  
maleate, or ( $\pm$ )-4-[4-[2-(5-methyl-2-phenyloxazol-4-  
yl)ethoxy]benzyl]isoxazolidin-3,5-dione, especially  
15 preferably pioglitazone hydrochloride.

In the present invention, the insulin sensitizer can  
be employed as a mixture of two or more species in an  
appropriate ratio.

20 The compound of the formula (I) or its salt is a known  
compound which is described in WO96/16938 and possesses a  
 $\beta$  3 adrenergic receptor stimulating activity, or a compound  
produced in accordance with an analogous method to a method  
25 described in WO96/16938. In the formula (I), groups having  
the term "lower" mean that these groups have 1 to 4 carbon  
atoms.

Examples of the preferred compound of the formula (I)  
or its salt includes  
30 2-[3-(7-methoxyindol-3-yl)-2-propylamino]-1-(3-  
chlorophenyl)ethanol;  
2-[3-(7-ethoxyindol-3-yl)-2-propylamino]-1-(3-  
chlorophenyl)ethanol;  
2-[3-(7-methoxycarbonylmethoxyindol-3-yl)-2-  
35 propylamino]-1-(3-chlorophenyl)ethanol;  
2-[3-(7-carboxymethoxyindol-3-yl)-2-propylamino]-1-(3-

chlorophenyl)ethanol; and their optical isomers or salts.

Among these, preferred is 2-[3-(7-carboxymethoxyindol-3-yl)-(2R)-2-propylamino]-(1R)-1-(3-chlorophenyl)ethanol, also called as 2-[[3-[(2R)-2-  
5 [[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1H-indol-7-yl]oxy]acetic acid (hereafter abbreviated as Compound A).

The compound of the formula (II) or its salt is a known  
10 compound which is described in JP-A H6(1994)-345731 and possesses a  $\beta$ 3 adrenergic receptor stimulating activity, or a compound produced in accordance with an analogous method to a method described in JP-A H6(1994)-345731. In the formula (II), "lower alkyl group" in "lower alkyl group"  
15 and "halogeno-lower alkyl group" means C<sub>1-3</sub> alkyl group.

Examples of the preferred compound of the formula (II) or its salt includes  
2-[(1R)-2-(indol-3-yl)-1-methylethylamino]-(1R)-1-(3-chlorophenyl)ethanol (hereafter abbreviated as Compound B)  
20 and its pharmacologically acceptable acid-addition salt.

The compound of the formula (III) or its salt is a known compound which is described in USP 5451677 and possesses a  $\beta$ 3 adrenergic receptor agonistic activity.

25 Examples of the preferred compound of the formula (III) or its salt includes

N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]benzenesulfonamide;

30 N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide;

N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide;  
35

N-[4-[2-[[2-hydroxy-3-(4-

- hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-(benzo-  
2,1,3-thiadiazol)sulfonamide;  
N-[4-[2-[[2-hydroxy-3-(4-  
hydroxyphenoxy)propyl]amino]ethyl]phenyl]-2-  
5 phenylethanesulfonamide;  
N-[4-[2-[[3-(4-fluorophenoxy)-2-  
hydroxypropyl]amino]ethyl]phenyl]-4-benzenesulfonamide;  
N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-  
hydroxy]propyl]amino]ethyl]phenyl]-2-  
10 naphthalenesulfonamide.

The compound of the formula (V) or its salt is a known compound which is described in WO99/01431 and possesses a  $\beta$ 3 agonistic activity. In the formula (V), groups having  
15 the term "lower" mean that these groups have 1 to 4 carbon atoms.

Examples of the preferred compound of the formula (V) or its salt includes

- (R)-N'-[5-[2-[2-(5,6,7,8-tetrahydro-9H-carbazol-2-  
20 yloxy)ethylamino]-1-hydroxyethyl]-2-hydroxyphenyl]-N,N-  
dimethylsulfamide hydrochloride.

The compound of the formula (VI) or its salt is a known compound which is described in WO97/23511 and possesses a  $\beta$ 3 agonistic activity. In the formula (VI), groups having  
25 the term "lower" mean that these groups have 1 to 4 carbon atoms.

Examples of the preferred compound of the formula (VI) or its salt includes

- ( $\pm$ )-N-[5-[2-[2-(9H-carbazol-2-yloxy)ethylamino]-1-  
30 hydroxyethyl]-2-hydroxyphenyl]methanesulfonamide  
hydrochloride;  
( $\pm$ )-N-[3-[2-[2-(9H-carbazol-2-yloxy)ethylamino]-1-  
hydroxyethyl]phenyl]methanesulfonamide hydrochloride;  
35 ( $\pm$ )-2-[N-[2-(9H-carbazol-2-yloxy)ethylamino]-1-  
phenylethanol hydrochloride; and their optical isomers.

Further, examples of the compound of the formula (V) or (VI), or its salt include AZ40140, etc.

Salts of the compound of the formula (I), (II), (III),  
5 (V) or (VI) include those similar to the salt of a compound of the formula (IV) mentioned above.

In the pharmaceutical composition of the present invention, combination of an insulin sensitizer and a  
10 compound of the formula (I) is preferable.

Preferred examples of the pharmaceutical composition of the present invention include  
1) a pharmaceutical composition comprising pioglitazone or  
15 its hydrochloride in combination with Compound A;  
2) a pharmaceutical composition comprising troglitazone in combination with Compound A;  
3) a pharmaceutical composition comprising rosiglitazone or its maleate in combination with Compound A.  
20

A pharmaceutical composition of the present invention and its active ingredient can be used as an agent for preventing or treating diabetes. Examples of the diabetes include insulin-dependent (type I) diabetes mellitus,  
25 noninsulin-dependent (type II) diabetes mellitus, etc. A pharmaceutical composition of the present invention and its active ingredient is especially preferably employed for noninsulin-dependent diabetes mellitus.

Further, a pharmaceutical composition of the present  
30 invention and its active ingredient can be used as an agent for treating impaired glucose tolerance. Referring to the definition of impaired glucose tolerance, WHO (World Health Organization) suggests a criterion in a 75g oral glucose tolerance test (75g OGTT). According to this criterion,  
35 impaired glucose tolerance means a condition wherein a fasting glucose level (glucose concentration in venous

plasma) is less than 140mg/dl, and a 2hr after glucose level (glucose concentration in venous plasma), when a 75g oral glucose tolerance test is conducted after an overnight fasting, ranges from 140 to 199 mg/dl.

5 Diabetes means a condition wherein a fasting glucose level (glucose concentration in venous plasma) is 140mg/dl or more, and a 2hr after glucose level (glucose concentration in venous plasma), when a 75g oral glucose tolerance test is conducted after an overnight fasting, is  
10 200 mg/dl or more.

Regarding the criterion of diabetes, new criteria are reported from ADA (American Diabetic Association) on 1997 and from WHO on 1998.

15 According to these reports, diabetes means a condition wherein a fasting glucose level (glucose concentration in venous plasma) is 126mg/dl or more, and a 2hr after glucose level (glucose concentration in venous plasma), when a 75g oral glucose tolerance test is conducted after an overnight fasting, is 200 mg/dl or more.

20 According to the above reports, impaired glucose tolerance means a condition wherein a fasting glucose level (glucose concentration in venous plasma) is less than 126mg/dl, and a 2hr after glucose level (glucose concentration in venous plasma), when a 75g oral glucose  
25 tolerance test is conducted after an overnight fasting, is 140mg/dl or more and less than 200 mg/dl.

According to the ADA reports, a condition wherein a fasting glucose level (glucose concentration in venous plasma) is 110mg/dl or more and less than 126mg/dl, is  
30 called IFG (Impaired Fasting Glucose). According to the WHO report, a condition; among this IFG (Impaired Fasting Glucose), wherein a 2hr after glucose level (glucose concentration in venous plasma), when a 75g oral glucose tolerance test is conducted after an overnight fasting, is  
35 less than 140mg/dl, is called IFG (Impaired Fasting Glycemia).



The pharmaceutical composition of the present invention and its active ingredient can be also used as an agent for preventing or treating diabetes, impaired glucose tolerance, IFG (Impaired Fasting Glucose), IFG (Impaired Fasting Glycemia), all of which is defined by the above new criteria. The pharmaceutical composition of the present invention and its active ingredient can also prevent progress to diabetes from impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycemia).

Further, a pharmaceutical composition of the present invention and its active ingredient can be also used as an agent for preventing or treating diseases such as hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypo-high-density-lipoproteinemia, postprandial hyperlipidemia, etc.), hyperinsulinemia, obesity (including body weight increase after stopping a smoking habit, after stopping alimentary therapy, or after stopping exercise), hyperphagia, hypertension, cardiovascular diseases (e.g., atherosclerosis, etc.), polycystic ovary syndrome, gestational diabetes, pancreatitis, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis, inflammatory bowel diseases (e.g., inflammatory colitis, ulcerative colitis), etc.; or syndromes (e.g., syndrome X, visceral fat obesity syndrome, etc.) having some of these diseases in combination.

Further, a pharmaceutical composition of the present invention and its active ingredient can be used as an agent for preventing or treating diabetic complications (e.g., retinopathy, nephropathy, neuropathy, macroangiopathy, diabetic hyperosmolar coma, infectious diseases (e.g., respiratory infection, urinary tract infection, gastrointestinal tract infection, dermal soft tissue infection, inferior limb infection), diabetic osteoporosis,

diabetic gangrene, xerostomia, lowered sense of hearing, myocardial infarction, angina pectoris, cerebrovascular disease (e.g., cerebral apoplexy, cerebral infarction) or peripheral circulatory disturbance, etc.).

5

Further, a pharmaceutical composition of the present invention and its active ingredient can be used as an agent for preventing or treating irritable bowel syndrome, acute or chronic diarrhea; or for ameliorating bellyache, nausea, vomiting, or dysphoria in epigastrium, each of which is accompanied by gastrointestinal ulcer, acute or chronic gastritis, biliary dyskinesia, or cholecystitis.

Further, a pharmaceutical composition of the present invention and its active ingredient possess an effect of ameliorating cachexia, namely an effect of ameliorating the systematic syndrome featuring progressive loss of body weight (inclusive of loss of body weight due to lipolysis and loss of body weight due to myolysis), anemia, edema, and anorexia in chronic diseases such as malignant tumor, tuberculosis, diabetes, blood dyscrasia, endocrine diseases, infectious diseases, and acquired immunodeficiency syndrome.

Further, a pharmaceutical composition of the present invention and its active ingredient can be used as an agent for preventing or treating TNF- $\alpha$  mediated inflammatory diseases. The TNF- $\alpha$  mediated inflammatory diseases mean inflammatory diseases which occur in the presence of TNF- $\alpha$  and can be treated by way of a TNF- $\alpha$  inhibitory action.

Examples of such inflammatory diseases include diabetic complications (e.g., retinopathy, nephropathy, neuropathy, macroangiopathy), rheumatoid arthritis, osteoarthritis of the spine, osteoarthritis, low back pain, gout, postoperative or traumatic inflammation, remission of swelling, neuralgia, laryngopharyngitis, cystitis,

hepatitis, pneumonia, gastric mucosal injury (including aspirin-induced gastric mucosal injury), etc.

5 A pharmaceutical composition of the present invention and its active ingredient have an apoptosis inhibitory activity, and can be used as an agent for preventing or treating diseases mediated by promotion of apoptosis.

10 Examples of the diseases mediated by promotion of apoptosis include viral diseases (e.g., AIDS, fulminant hepatitis), neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration), myelodysplasia (e.g., aplastic anemia), ischemic diseases (e.g., myocardial infarction, cerebral apoplexy), hepatic  
15 diseases (e.g., alcoholic hepatitis, hepatitis B, hepatitis C), joint-diseases (e.g., osteoarthritis), atherosclerosis, etc.

20 Further, a pharmaceutical composition of the present invention and its active ingredient can be used for reducing visceral fats, inhibiting accumulation of visceral fats, ameliorating glucose metabolism, ameliorating lipid metabolism, ameliorating insulin resistance, inhibiting production of oxidized LDL, ameliorating lipoprotein  
25 metabolism, ameliorating coronary artery metabolism, preventing or treating cardiovascular complications, preventing or treating heart failure complications, lowering blood remnant, preventing or treating anovulation, preventing or treating hirsutism, preventing or treating  
30 hyperandrogenism, etc.

A pharmaceutical composition of the present invention and its active ingredient possess an action of controlling appetite, and thus can be used for treating emaciation or refusal of food.

35

A pharmaceutical composition of the present invention

and its active ingredient can be used for secondary prevention and for inhibition in progress, both of various diseases described above (e.g., cardiovascular events such as myocardial infarction, etc.).

5 Further, a pharmaceutical composition of the present invention and its active ingredient can be used in combination with midazolam, ketoconazole, etc.

10 A pharmaceutical composition of the present invention can be obtained by combining active ingredients, an insulin sensitizer and at least one member selected from the group consisting of a compound of the formula (I) or its salt, a compound of the formula (II) or its salt, a compound of the formula (III) or its salt, a compound of the formula (V) or its salt, and a compound of the formula (VI) or its salt (hereafter also abbreviated as compound (I) to (III), (V), (VI), respectively). These active ingredients may be subjected to pharmaceutical manufacturing processes by admixing separately or concomitantly with pharmaceutically acceptable carriers in accordance with per se known means [conventional means in fields of pharmaceutical manufacturing techniques, for instance, means described in the Pharmacopoeia of Japan (e.g., Thirteenth Edition, etc.)].

25 Examples of dosage forms of a pharmaceutical composition of the present invention or its respective active ingredients include oral dosage forms such as tablets, capsules (including soft capsules and microcapsules), powders, granules, syrups, etc.; and non-oral dosage forms such as injections (e.g., subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, etc.), external application forms (e.g., nasal spray preparations, transdermal preparations, ointments, etc.), 30 suppositories (e.g., rectal suppositories, vaginal

suppositories, etc.), pellets, drip infusions, sustained-release preparations, etc.

Methods of producing oral dosage forms and non-oral dosage forms are specifically explained below.

Oral dosage forms are produced by adding to the active ingredient(s), for instance, an excipient (e.g., lactose, sucrose, starch, D-mannitol, xylitol, sorbitol, erythritol, crystalline cellulose, light silicic anhydride, etc.), a disintegrator (e.g., calcium carbonate, starch, carboxymethylcellulose, carboxymethylcellulose calcium, low-substituted hydroxypropylcellulose, croscarmellose sodium, carboxymethylstarch sodium, light silicic anhydride, etc.), a binder (e.g.,  $\alpha$ -starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, crystalline cellulose, methylcellulose, sucrose, D-mannitol, trehalose, dextrin, etc.), or a lubricant (e.g., talc, magnesium stearate, calcium stearate, talc, colloidal silica, polyethylene glycol 6000, etc.), and then compressing and molding the resulting mixture. To the oral dosage form, acids such as hydrochloric acid, phosphoric acid, malonic acid, succinic acid, DL-malic acid, tartaric acid, maleic acid, fumaric acid, citric acid, etc.; or bases such as sodium carbonate, sodium hydrogencarbonate, sodium citrate, sodium tartrate, etc. can be added for the purpose of promoting dissolution of the active ingredient(s).

The oral dosage forms can be coated, by the per se known method, for masking the taste or for enteric dissolution or sustained release. Examples of a coating material that can be employed includes, enteric coating polymers such as cellulose acetate phthalate, methacrylic acid copolymer L, methacrylic acid copolymer LD, methacrylic acid copolymer S, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, etc.; gastric coating

polymers such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E, etc.; water-soluble polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, etc.; water-insoluble  
5 polymers such as ethylcellulose, aminoalkyl methacrylate copolymer RS, ethylacrylate-methylmethacrylate copolymer, etc.; wax, etc. When coating is carried out, plasticizers such as polyethylene glycol, etc.; and sunscreens such as titanium oxide, iron sesquioxide, etc. can be employed  
10 together with the above coating material.

Injectons can be produced by dissolving, suspending or emulsifying the active ingredient(s) in an aqueous vehicle (e.g., distilled water, physiological saline,  
15 Ringer's solution, etc.) or an oily vehicle (e.g., vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc.; or propylene glycol, macrogol, tricaprilyn, etc.) together with a dispersant (e.g., Tween 80 (produced by Atlas Powder, U.S.A.), HCO 60 (produced by Nikko  
20 Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g., sodium chloride, glycerol, D-sorbitol, D-mannitol, xylitol,  
25 glucose, fructose, etc.) etc.

If desired, also employed are additives such as a solubilizer (e.g., sodium salicylate, sodium acetate, polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane,  
30 cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.), a suspending agent (e.g., surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate,  
35 etc.; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium,

methyleellulose, hydroxymethyleellulose,  
hydroxyethylcellulose, hydroxypropyleellulose, etc.), a  
buffering agent (e.g., buffer solutions such as phosphate,  
acetate, carbonate, citrate, etc.), a stabilizer (e.g.,  
5 human serum albumin, etc.), a soothing agent (e.g.,  
propylene glycol, lidocaine hydrochloride, benzyl alcohol,  
etc.), an antiseptic (e.g., p-hydroxybenzoic acid esters,  
chlorobutanol, benzalkonium chloride, benzyl alcohol,  
phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.),  
10 etc.

External application forms can be produced by  
processing the active ingredient(s) into a solid, semi-  
solid or liquid composition. For instance, a solid  
15 composition is produced by processing the active  
ingredient(s), either as such or in admixture with an  
excipient (e.g., lactose, D-mannitol, starch,  
microcrystalline cellulose, sucrose, etc.), a thickener  
(e.g., natural gums, cellulose derivatives, acrylic acid  
20 polymers, etc.), etc., into powders. The above liquid  
composition is produced in substantially the same manner  
as in the case of injections. The semi-solid composition  
is preferably provided in a hydrous or oily gel form or an  
ointment form. These compositions may optionally contain  
25 a pH control agent (e.g., phosphoric acid, citric acid,  
hydrochloric acid, sodium hydroxide, etc.), an antiseptic  
(e.g., p-hydroxybenzoic acid esters, chlorobutanol,  
benzalkonium chloride, benzyl alcohol, phenethyl alcohol,  
dehydroacetic acid, sorbic acid, etc.), etc.

30

Suppositories can be produced by processing the active  
ingredient(s) into an oily or aqueous composition, whether  
solid, semi-solid or liquid. Examples of oleaginous bases  
that can be used in producing the composition include higher  
35 fatty acid glycerides [e.g., cacao butter, Witepsols (huels  
Aktiengesellschaft, Germany), etc.], medium-chain fatty

acid triglycerides [e.g., Migriols(huels Aktiengesellschaft, Germany), etc.], vegetable oils (e.g., sesame oil, soybean oil, cottonseed oil, etc.), etc. Examples of aqueous bases include polyethylene glycols, propylene glycol, etc. Further, examples of the aqueous gel bases include natural gums, cellulose derivatives, vinyl polymers, and acrylic acid polymers, etc.

The method for administering a pharmaceutical composition of the present invention is not limited as long as an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] are combined at the time of administration. Examples of such methods include 1) administration of a single preparation prepared from an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] at the same time; 2) concomitant administration of two kinds of preparations prepared from an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] separately by the same administration route; 3) staggered administration of two kinds of preparations prepared from an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] separately by the same administration route; 4) concomitant administration of two kinds of preparations prepared from an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] separately by different administration routes; 5) staggered administration of two kinds of preparations prepared from an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] separately by different administration routes (e.g., administration of an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] in this order, or reverse order); etc. Among others, the above 2) and 3) are preferred.

Preferred embodiments include processing an insulin sensitizer and any of compounds [I] to [III], [V] and [VI] separately into oral dosage forms such as tablets, and administering the oral dosage forms concomitantly or with



a staggered time.

A pharmaceutical composition of the present invention and its active ingredient are low in potential toxicity, and can be safely used in mammals (e.g., human, mouse, rat, rabbit, dog, cat, bovine, equine, swine, monkey, etc.), either orally or non-orally.

The dosage of a pharmaceutical composition of the present invention may be appropriately determined with reference to the dosage recommended for the respective active ingredient(s), and can be selected appropriately according to the subject, the age and body weight of the subject, current clinical status, administration time, dosage form, method of administration, combination of the drug(s), etc.

The dosage of an insulin sensitizer and compounds [I] to [III], [V] and [VI] can be selected appropriately based on clinically used dosage.

For administration of an insulin sensitizer to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.01 to 1000 mg, preferably 0.1 to 500 mg. This dose can be administered once to several times a day. Especially, when pioglitazone hydrochloride is employed as the insulin sensitizer, the dose of pioglitazone hydrochloride per day is usually 7.5 to 60 mg, preferably 15 to 45 mg. When troglitazone is employed as the insulin sensitizer, the dose of troglitazone per day is usually 100 to 1000 mg, preferably 200 to 600 mg. When rosiglitazone (or its maleate) is employed as the insulin sensitizer, the dose of rosiglitazone per day is usually 1 to 12 mg, preferably 2 to 8 mg.

For administration of compounds [I] to [III], [V] and [VI] to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.1 to 500 mg, preferably 0.1 to 200 mg, more preferably 0.1 to 50 mg. Especially, the dose of compound A per day is usually 0.1

to 10 mg, preferably 0.2 to 3 mg.

5 The proportion of an insulin sensitizer and compounds  
[I] to [III], [V] and [VI] in a pharmaceutical composition  
of the present invention can be selected appropriately  
according to the subject, the age and body weight of the  
subject, current clinical status, administration time,  
dosage form, method of administration, combination of the  
10 drug(s), etc. For instance, compounds [I] to [III], [V]  
and [VI] are used in a proportion of usually about 0.005  
to 1 weight part and preferably about 0.001 to 0.2 weight  
parts relative to one weight part of an insulin sensitizer.

15 A pharmaceutical composition of the present invention  
possesses an enhanced blood sugar lowering action as  
compared with administration of an insulin sensitizer or  
any of compounds [I] to [III], [V] and [VI] alone.

Further, a pharmaceutical composition of the present  
invention possesses an enhanced blood lipid lowering action  
20 or blood insulin lowering action as compared with  
administration of an insulin sensitizer or any of compounds  
[I] to [III], [V] and [VI] alone.

Further, a pharmaceutical composition of the present  
invention possesses an excellent effect of treating  
25 diabetes, and therefore, the amount of drugs used can be  
reduced as compared with administration of an insulin  
sensitizer or any of compounds [I] to [III], [V] and [VI]  
alone.

Further, when the pharmaceutical composition of the  
30 present invention is administered to a diabetic patient,  
a tendency of decrease in the patient's body weight as  
compared with administration of an insulin sensitizer or  
any of compounds [I] to [III], [V] and [VI] alone is  
observed.

35

Referring to a pharmaceutical composition of the

present invention, concomitant drugs which do not interfere with an insulin sensitizer or compounds [I] to [III], [V] and [VI] can be used for the purpose of "enhancing the diabetes treating effects of an insulin sensitizer or compounds [I] to [III], [V] and [VI]", "reducing the dose of an insulin sensitizer or compounds [I] to [III], [V] and [VI]", "reducing the side effects of an insulin sensitizer or compounds [I] to [III], [V] and [VI]", etc. Examples of the concomitant drugs include "agents for treating diabetes", "agents for treating diabetic complications", "anti-obesity agents", "agents for treating hypertension", "agents for treating hyperlipidemia", "diuretics", etc. Further, a dietetic therapy (therapy by restriction of nutrition or calories) or a therapeutic exercise can be employed at the time of using a pharmaceutical composition of the present invention.

Examples of the "agents for treating diabetes" include insulin, insulin secretion enhancers, biguanides,  $\alpha$ -glucosidase inhibitors, etc.

Insulin means any and all substances having an insulin action, and exemplified by, for instance, animal insulin extracted from bovine or porcine pancreas; semi-synthesized human insulin which is enzymatically synthesized from insulin extracted from porcine pancreas; and human insulin synthesized by genetic engineering techniques typically using Escherichia coli or yeasts; etc.

Further, as insulin employed are insulin-zinc containing 0.45 to 0.9 (w/w) % of zinc; protamine-insulin-zinc produced from zinc chloride, protamine sulfate and insulin; etc. Insulin may be in the form of its fragments or derivatives (e.g., INS-1). Insulin may be insulin-like substances (e.g., L83281, insulin agonists).

While insulin is available in a variety of types such as super immediate-acting, immediate-acting, bimodal-

acting, intermediate-acting, long-acting, etc., these types can be appropriately selected according to the patient's condition.

5 Use of a pharmaceutical composition of the present invention in combination with insulin enables reduction of the dose of insulin as compared with the dose at the time of administration of insulin alone. Therefore, risk of blood vessel complication and hypoglycemia induction, both of which are problems with large amounts of insulin  
10 administration, is low.

Since a pharmaceutical composition of the present invention possesses an excellent effect of treating diabetes, a satisfactory effect of treating diabetes can be obtained even if the dose of insulin is reduced as  
15 compared with administration of insulin alone.

Examples of the insulin secretion enhancers include sulfonylureas. Specific examples of the sulfonylureas include tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide and its ammonium salt,  
20 glibenclamide, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibornuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcyclamide, glimepiride, etc.

25 In addition to the above, examples of the insulin secretion enhancers include nateglinide (AY-4166), calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylylcarbonyl)propionate dihydrate (mitiglinide, KAD-1229), repaglinide, etc.

30 Examples of the biguanides include phenformin, metformin, buformin, etc.

Examples of the  $\alpha$ -glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate, etc.

35 In addition to the above, examples of the "agents for treating diabetes" include ergoset, pramlintide, leptin, BAY-27-9955, T-1095, etc.

For administration of the "agents for treating diabetes" to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.1 to 2500 mg, preferably 0.5 to 1000 mg. This dose can be administered once to several times a day.

For administration (usually administration in the form of injections) of insulin to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 10 to 100 U (Units), preferably 10 to 80 U (Units). This dose can be administered once to several times a day.

For administration of insulin secretion enhancers to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.1 to 1000 mg, preferably 1 to 100 mg. This dose can be administered once to several times a day.

For administration of biguanides to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 10 to 2500 mg, preferably 100 to 1000 mg. This dose can be administered once to several times a day.

For administration of  $\alpha$ -glucosidase inhibitors to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.1 to 400 mg, preferably 0.6 to 300 mg. This dose can be administered once to several times a day.

Examples of the "agents for treating diabetic complications" include aldose reductase inhibitors, glycation inhibitors, protein kinase C inhibitors, etc.

Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; imirestat; zenarestat; 6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; 1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-

16209); CT-112; NZ-314; ARI-509; etc.

Examples of the glycation inhibitors include pimagedine, etc.

5 Examples of the protein kinase C inhibitors include NGF, LY-333531, etc.

10 In addition to the above, examples of the "agents for treating diabetic complications" include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentaenoate, memantine, pimagedline (ALT-711), etc.

15 For administration of the "agents for treating diabetic complications" to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.1 to 2000 mg. This dose can be administered once to several times a day.

20 For administration of aldose reductase inhibitors to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 1 to 1000 mg. This dose can be administered once to several times a day.

For administration of glycation inhibitors to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 1 to 2000 mg. This dose can be administered once to several times a day.

25 For administration of protein kinase C inhibitors to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.1 to 100 mg. This dose can be administered once to several times a day.

30 Examples of the "agents for treating obesity" include lipase inhibitors, anorectics, etc.

Examples of the lipase inhibitors include orlistat, etc.

35 Examples of the anorectics include dexfenfluramine, fluoxetine, sibutramine, baiamine, etc.

For administration of the "agents for treating

obesity" to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.01 to 1000 mg, preferably 0.1 to 1000 mg. This dose can be administered once to several times a day.

- 5 For administration of lipase inhibitors to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.1 to 1000 mg. This dose can be administered once to several times a day.

- 10 For administration of anorectics to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.01 to 1000 mg, preferably 0.1 to 500 mg. This dose can be administered once to several times a day.

- 15 Examples of the "agents for treating hypertension" include angiotensin converting enzyme inhibitors, calcium antagonists, potassium channel openers, angiotensin II antagonists, etc.

- 20 Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, manidipine, etc.

- 25 Examples of the calcium antagonists include nifedipine, amlodipine, efonidipine, nicardipine, etc.

Examples of the potassium channel openers include levromakalim, L-27152, AL 0671, NIP-121, etc.

- 30 Examples of the angiotensin II antagonists include losartan, candesartan cilexetil, valsartan, irbesartan, (5-methyl-2-oxo-1,3-dioxoran-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazol-5-carboxylate (CS-866), E4177, etc.

- 35 For administration of the "agents for treating hypertension" to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.01 to

1000 mg. This dose can be administered once to several times a day.

For administration of angiotensin converting enzyme inhibitors to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.01 to 500 mg, preferably 0.1 to 100 mg. This dose can be administered once to several times a day.

For administration of calcium antagonists to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.1 to 500 mg, preferably 1 to 200 mg. This dose can be administered once to several times a day.

For administration of potassium channel openers to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.01 to 1000 mg. This dose can be administered once to several times a day.

For administration of angiotensin II antagonists to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.1 to 500 mg, preferably 1 to 100 mg. This dose can be administered once to several times a day.

Examples of the "agents for treating hyperlipidemia" include, HMG-CoA reductase inhibitors, fibrate compounds, etc.

Examples of the HMG-CoA reductase inhibitors include pravastatin and its sodium salt, cerivastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, itavastatin, ZD-4522, etc.

Examples of the fibrate compounds include bezafibrate, beclofibrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

For administration of the "agents for treating hyperlipidemia" to an adult diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.01 to



3000 mg, preferably 1 to 2000 mg. This dose can be administered once to several times a day.

For administration of HMG-CoA reductase inhibitors to an adult diabetic patient (body weight: 50 kg), the dose  
5 per day is usually 0.01 to 100 mg, preferably 0.5 to 50 mg.

This dose can be administered once to several times a day.

For administration of fibrate compounds to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 1 to 2000 mg, preferably 10 to 1500 mg. This dose  
10 can be administered once to several times a day.

Examples of the "diuretics" include xanthine derivative preparations, thiazide preparations, antialdosterone preparations, carbonate dehydratase  
15 inhibitors, chlorbenzenesulfonamide preparations, etc.

Examples of the xanthine derivative preparations include theobromine and sodium salicylate, theobromine and calcium salicylate, etc.

Examples of the thiazide preparations include  
20 ethiazide, cyclopenthiazide, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide, etc.

Examples of the antialdosterone preparations include  
25 spironolactone, triamterene, etc.

Examples of the carbonate dehydratase inhibitors include acetazolamide, etc.

Examples of the chlorbenzenesulfonamide preparations include chlorthalidone, mefruside, indapamide, etc.

30 In addition to the above, examples of the "diuretics" include azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, furosemide, etc.

For administration of the "diuretics" to an adult  
35 diabetic patient (body weight: 50 kg), for instance, the dose per day is usually 0.01 mg to 100 g, preferably 0.05

mg to 10 g. This dose can be administered once to several times a day.

For administration of xanthine derivative preparations to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.1 to 100 g, preferably 0.5 to 10 g. This dose can be administered once to several times a day.

For administration of thiazide preparations to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 0.01 to 2000 mg, preferably 0.05 to 500 mg. This dose can be administered once to several times a day.

For administration of antialdosterone preparations to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 1 to 2000 mg, preferably 10 to 1000 mg. This dose can be administered once to several times a day.

For administration of carbonate dehydratase inhibitors to an adult (body weight: 50 kg), the dose per day is usually 10 to 5000 mg, preferably 50 to 2000 mg. This dose can be administered once to several times a day.

For administration of chlorbenzenesulfonamide preparations to an adult diabetic patient (body weight: 50 kg), the dose per day is usually 1 to 2000 mg, preferably 10 to 1000 mg. This dose can be administered once to several times a day.

The concomitant drugs mentioned above can be used as a mixture of two or more species optionally selected. Specific examples of combination when two kinds of concomitant drugs are used in combination include "combination of an insulin secretion enhancer and a biguanide", "combination of an insulin secretion enhancer and an  $\alpha$ -glucosidase inhibitor", "combination of insulin and a biguanide", "combination of insulin and an  $\alpha$ -glucosidase inhibitor", etc.

The administration method of a pharmaceutical

composition of the present invention and a concomitant drug is not limited as long as these are used in combination at the time of administration.

5 The proportion of an a pharmaceutical composition of the present invention and a concomitant drug can be selected appropriately according to the subject, the age and body weight of the subject, current clinical status, administration time, dosage form, administration method, etc. For instance, a concomitant drug is used in a  
10 proportion of 0.0001 to 10000 weight parts relative to one weight part of a pharmaceutical composition of the present invention.

Use of at least one species among compounds [I] to  
15 [III], [V] and [VI] in combination with at least one species among the concomitant drug mentioned above, without using an insulin sensitizer, provides various pharmaceutical effects referred to as those for a pharmaceutical composition of the present invention, such as an excellent  
20 effect of treating diabetes.

Specific combination of compounds [I] to [III], [V] and [VI] with the above concomitant drugs includes, for instance, "combination of Compound A and an insulin", "combination of Compound B and an insulin", "combination  
25 of Compound A and an insulin secretion enhancer (preferably sulfonylureas such as glibenclamide; repaglinide, nateglinide, mitiglinide, etc.)", "combination of Compound B and an insulin secretion enhancer (preferably sulfonylureas such as glibenclamide; repaglinide,  
30 nateglinide, mitiglinide, etc.)", "combination of Compound A and a biguanide (preferably metformin, etc.)", "combination of Compound B and a biguanide (preferably metformin, etc.)", "combination of Compound A and an  $\alpha$ -glucosidase inhibitor (preferably acarbose, etc.)",  
35 "combination of Compound B and an  $\alpha$ -glucosidase inhibitor (preferably acarbose, etc.)", "combination of Compound A

and a HMG-CoA reductase inhibitor (preferably pravastatin or its sodium salt, cerivastatin or its sodium salt, atorvastatin, etc.)", "combination of Compound B and a HMG-CoA reductase inhibitor (preferably pravastatin or its sodium salt, cerivastatin or its sodium salt, atorvastatin, etc.)", etc.

When any of compounds [I] to [III], [V] and [VI] is used alone, the method of use in the above mentioned pharmaceutical composition of the present invention can be appropriately applied, and a known method of use can also be appropriately applied.

Use of a pharmaceutical composition of the present invention or its active ingredient (e.g., pioglitazone hydrochloride, rosiglitazone maleate, Compound A, Compound B, etc.) in combination with the above concomitant drugs (e.g., insulin; insulin secretion enhancers such as sulfonylureas; biguanides such as metformin; HMG-CoA reductase inhibitors such as cerivastatin sodium salt, etc.) provides enhancement in various pharmaceutical effects referred to as those for a pharmaceutical composition of the present invention, such as effects of treating diabetes, hyperlipidemia, hyperinsulinemia, etc.

Further, such combination enables reduction in the dose of "a pharmaceutical composition of the present invention or its active ingredient (e.g., pioglitazone hydrochloride, rosiglitazone maleate, Compound A, Compound B, etc.)" or "concomitant drugs (e.g., insulin; insulin secretion enhancers such as sulfonylureas; biguanides such as metformin; HMG-CoA reductase inhibitors such as cerivastatin sodium salt, etc.)" as compared with the dose at the time of administration of these alone.

The blood sugar lowering effect of a pharmaceutical composition in the present invention can be evaluated by determining concentration of glucose or Hb (hemoglobin)A<sub>1c</sub>.

in venous blood plasma in the subject before and after administration, and then comparing the obtained concentration between before administration and after administration. HbA<sub>1c</sub> means glycosylated hemoglobin, and is gradually produced in response to blood glucose concentration. Therefore, HbA<sub>1c</sub> is thought important as an index of blood sugar control which is not easily influenced by rapid blood sugar changes in diabetic patients.

#### 10 BEST MODE FOR CARRYING OUT THE INVENTION

The following Reference Examples and Examples are intended to describe the present invention in further detail and should by no means be construed as defining the scope of the invention.

##### 15 Reference Example 1

A fluidized-bed granulating and drying machine (produced by Powerex) was charged with 2479.5 g of pioglitazone hydrochloride (2250 g in terms of pioglitazone), 13930.5 g of lactose and 540 g of carboxymethylcellulose calcium (carmellose calcium), followed by mixing at the preheating temperature and spraying 7500 g of an aqueous solution containing 450 g of hydroxypropylcellulose to yield granules. 16820 g of the granules were processed with cutter-mill (produced by Showa Kagaku Kikai Kousakusho) to yield milled granules. 16530 g of the milled granules, 513 g of carmellose calcium and 57 g of magnesium stearate were mixed to yield mixed powders by using a tumbling mixer (produced by Showa Kagaku Kikai Kousakusho). 16800 g of the mixed powders were tabletted by using a tableting machine (produced by Kikusui Seisakusho) to yield 140000 tablets having the following composition and each containing 15 mg of pioglitazone.

Composition per tablet (Unit: mg):

1) Pioglitazone hydrochloride	16.53
2) Lactose	92.87
3) Carmellose calcium	7.2

4) Hydroxypropylcellulose	3.0
5) <u>Magnesium stearate</u>	<u>0.4</u>

Total: 120.0

## 5 Reference Example 2

In the similar manner to Reference Example 1, 140000 tablets having the following composition and each containing 30 mg of pioglitazone were obtained.

Composition per tablet (Unit: mg):

10	1) Pioglitazone hydrochloride	33.06
	2) Lactose	76.34
	3) Carmellose calcium	7.2
	4) Hydroxypropylcellulose	3.0
	5) <u>Magnesium stearate</u>	<u>0.4</u>

15

Total: 120.0

## Reference Example 3

In the similar manner to Reference Example 2, 140000 tablets having the following composition and each containing 45 mg of pioglitazone were obtained.

Composition per tablet (Unit: mg):

20	1) Pioglitazone hydrochloride	49.59
	2) Lactose	114.51
	3) Carmellose calcium	10.8
25	4) Hydroxypropylcellulose	4.5
	5) <u>Magnesium stearate</u>	<u>0.6</u>

Total: 180.0

## Example 1

30 When pioglitazone hydrochloride (30 mg/day, oral administration) and Compound A (0.5 mg/day, oral administration) are concomitantly administered to a NIDDM patient over the period of 8 weeks, an excellent blood glucose lowering action is observed.

35

## Example 2

When pioglitazone hydrochloride (30 mg/day, oral administration) and Compound B (0.5 mg/day, oral administration) are concomitantly administered to a NIDDM patient over the period of 8 weeks, an excellent blood glucose lowering action is observed.

### Example 3

Twenty three Wistar fatty rats, genetically obese and noninsulin-dependent diabetic (type 2 diabetic) models, (16 weeks old, male) were divided into Groups A to D.

To Group A (6 rats), a 0.5% (w/w) methylcellulose/physiological saline suspension (2 ml/kg body weight/day) and a 0.5% (w/w) tragacanth gum aqueous suspension (2 ml/kg body weight/day) were orally administered for 14 days. This group was considered as a control group.

To Group B (6 rats), a 0.5% (w/w) methylcellulose/physiological saline suspension (2 ml/kg body weight/day) containing pioglitazone hydrochloride (1 mg/kg body weight/day) and a 0.5% (w/w) tragacanth gum aqueous suspension (2 ml/kg body weight/day) were orally administered for 14 days.

To Group C (6 rats), a 0.5% (w/w) methylcellulose/physiological saline suspension (2 ml/kg body weight/day) and a 0.5% (w/w) tragacanth gum aqueous suspension (2 ml/kg body weight/day) containing Compound A (0.1 mg/kg body weight/day) were orally administered for 14 days.

To Group D (5 rats), a 0.5% (w/w) methylcellulose/physiological saline suspension (2 ml/kg body weight/day) containing pioglitazone hydrochloride (1 mg/kg body weight/day) and a 0.5% (w/w) tragacanth gum aqueous suspension (2 ml/kg body weight/day) containing Compound A (0.1 mg/kg body weight/day) were orally administered for 14 days.

The rats were allowed to take food freely.

After completion of administration over 14 days, blood

was collected from the tail vein of the rats, and plasma was separated. Then, glucose and triglyceride in the plasma were quantified by L Type Wako Glu 2 (Wako Pure Chemical Industries, Ltd.) and L Type Wako TG · H (Wako Pure Chemical Industries, Ltd.), respectively. The results are shown in Table 1.

After completion of administration over 14 days, body weights of the rats were determined. The results are shown in Table 2.

In the following tables, "pio" and "cpd A" mean pioglitazone hydrochloride and Compound A, respectively. Figures in the tables represent mean  $\pm$  SD (standard deviation).

[Table 1]

	Plasma glucose (mg/dl)	Plasma triglyceride (mg/dl)
Group A(Control)	352.1 $\pm$ 89.0	362.9 $\pm$ 76.6
Group B(pio)	235.0 $\pm$ 56.6	143.1 $\pm$ 33.0
Group C(cpd A)	230.6 $\pm$ 88.1	210.6 $\pm$ 125.4
Group D(pio+cpd A)	148.5 $\pm$ 20.1	76.2 $\pm$ 14.2

[Table 2]

	Body weight (g)
Group A(Control)	605.4 $\pm$ 34.0
Group B(pio)	641.9 $\pm$ 15.9
Group C(cpd A)	595.3 $\pm$ 26.0
Group D(pio+cpd A)	620.2 $\pm$ 24.2

As shown in Table 1, use of pioglitazone hydrochloride in combination with Compound A provided excellent effects of lowering a plasma glucose and a plasma triglyceride.

Further, as shown in Table 2, use of pioglitazone hydrochloride in combination with Compound A unexpectedly provided an effect of inhibiting a body weight increase.

Namely, the body weight increase in Group D was expected to be 26.4 (36.5 - 10.1) g because of the fact that



the body weight increase in Group B was 36.5 (641.9 - 605.4) g and the body weight increase in Group C was -10.1 (595.3 - 605.4) g. Actually, the body weight increase in Group D was unexpectedly low and was 14.8 (620.2 - 605.4) g.

5

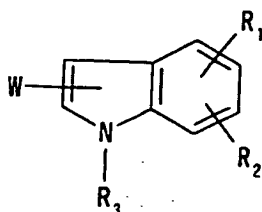
#### Industrial Applicability

- A pharmaceutical composition of the present invention possesses an enhanced blood sugar lowering action, blood
- 10 lipid lowering action or blood insulin lowering action as compared with administration of an insulin sensitizer or any of compounds [I] to [III], [V] and [VI] alone.

## CLAIMS

1. A pharmaceutical composition which comprises an insulin sensitizer in combination with at least one member selected from the group consisting of

- 5 1) a compound of the formula [I] :



wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

- 15 (a) a group of the formula :  $-Xa-Ra$

wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;

- (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

20 wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,

- (c) a group of the formula :  $-O(CH_2)_r-Rc$

25 wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$

wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

- 30 (d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

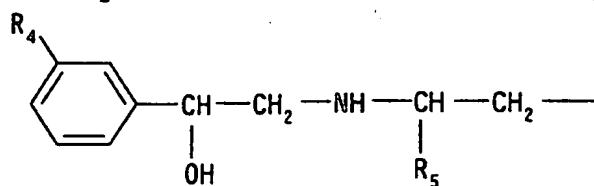
wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,

R<sub>2</sub> represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above (b) or (c), or combines with R<sub>1</sub> to form the above

5 methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxycarbonyl group,

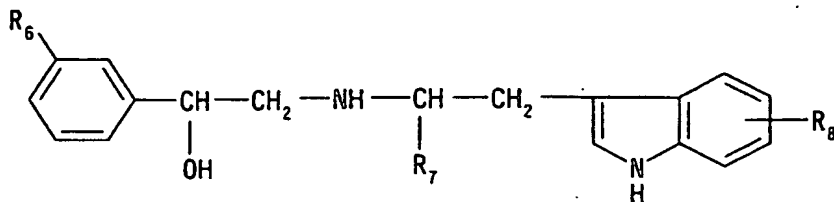
R<sub>1</sub> represents hydrogen atom or a lower alkyl group,

W represents a group of the formula which bonds to the 2-  
10 or 3-position of the indole ring in the formula [I]:



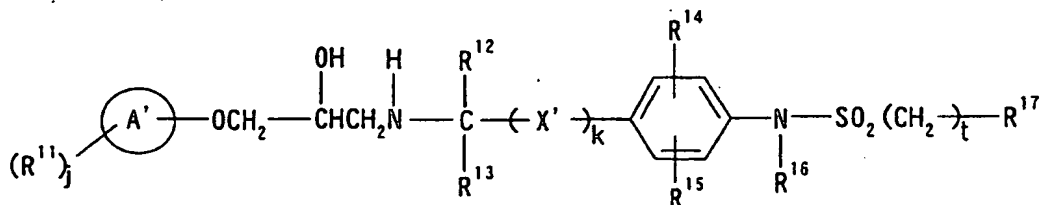
wherein R<sub>4</sub> represents a halogen atom or a halogeno lower alkyl group, R<sub>5</sub> represents a lower alkyl group, or a salt thereof:

15 2) a compound of the formula [II] :



wherein R<sub>6</sub> represents a halogen atom or a halogeno lower alkyl group, R<sub>7</sub> represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group, R<sub>8</sub> represents  
20 hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



wherein j represents an integer of 0 to 7,

25 k represents 0 or 1,

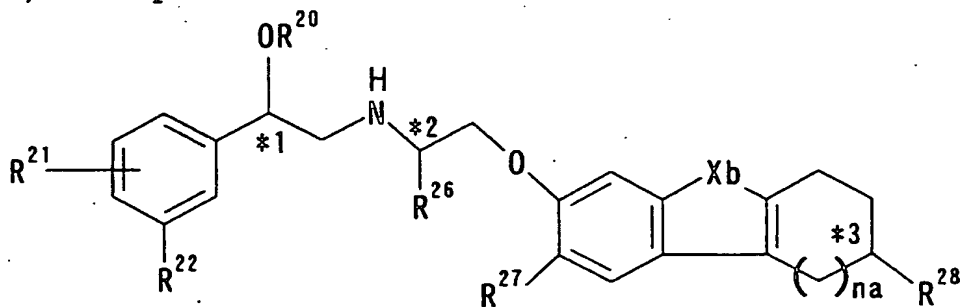
- t represents an integer of 0 to 3.
- ring A' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;
- or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;
- R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;
- X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;
- R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;
- R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;
- R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub> wherein R<sup>11</sup> and j have the same meanings as above;
- ring B' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic

ring containing 1 to 3 hetero atoms selected from O, S and N;

$R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$  alkyl substituted by hydroxy, halogen,  $CO_2H$ ,  $C_{1-6}$  alkoxy-carbonyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkoxy, or phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;

$R^{19}$  represents  $R^{18}$ ,  $NHR^{18}$  or  $NR^{18}$  wherein  $R^{18}$  has the same meaning as above, or a salt thereof;

4) a compound of the formula [V] :



wherein  $R^{20}$  represents hydrogen atom or methyl group,

$R^{21}$  represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,

$R^{22}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{23}$ ,  $SO_2NR^{24}R^{24'}$  or nitro group,

$R^{23}$  represents hydrogen atom, methyl group,  $SO_2NR^{25}$ , formyl group or  $CONHR^{26'}$ ,

$R^{25}$  represents a lower alkyl group, benzyl group or  $NR^{24}R^{24'}$ ,

$R^{24}$  and  $R^{24'}$  are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

$R^{26'}$  represents hydrogen atom or a lower alkyl group,

$R^{26}$  represents hydrogen atom or a lower alkyl group,  $na$  is 1 or 2,

$Xb$  represents secondary nitrogen atom, O or S,

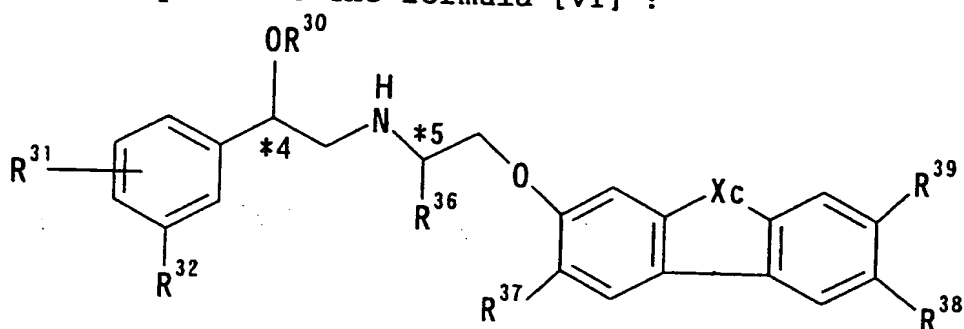
one of  $R^{27}$  or  $R^{28}$  is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when  $na$  is 1,

$R^{28}$  is hydrogen atom, and  $R^{27}$  is hydrogen atom, amino group,

acetylamino group or hydroxy group, when  $na$  is 2,

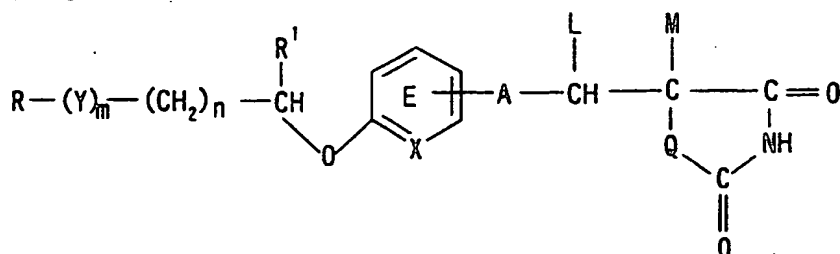
\*1 represents an asymmetric carbon atom,  
 \*2 and \*3 represent an asymmetric carbon atom when  $R^{26}$  and  $R^{28}$  are respectively not hydrogen atom, or a salt thereof;  
 and

5 5) a compound of the formula [VI] :



wherein  $R^{30}$  represents hydrogen atom or methyl group,  
 $R^{21}$  represents hydrogen atom, a halogen atom, hydroxy group,  
 benzyloxy group, amino group or hydroxymethyl group,  
 10  $R^{32}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  
 $SO_2NR^{34}R^{34'}$  or nitro group,  
 $R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl  
 group or  $CONHR^{36'}$ ,  
 $R^{35}$  represents a lower alkyl group, benzyl group or  $NR^{34}R^{34'}$ ,  
 15  $R^{34}$  and  $R^{34'}$  are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,  
 $R^{36'}$  represents hydrogen atom or a lower alkyl group,  
 $R^{36}$  represents hydrogen atom or a lower alkyl group,  
 $Xc$  represents secondary nitrogen atom, O, S or methylene  
 20 group,  
 $R^{39}$  is hydrogen atom, one of  $R^{37}$  or  $R^{38}$  is hydrogen atom, and  
 the other is hydrogen atom, amino group, acetylamino group  
 or hydroxy group, when  $Xc$  is secondary nitrogen atom, O or  
 S,  
 25  $R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom,  
 amino group, acetylamino group or hydroxy group, when  $Xc$   
 is methylene group,  
 \*4 represents an asymmetric carbon atom,  
 \*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower  
 30 alkyl group, or a salt thereof.

2. A pharmaceutical composition according to claim 1, wherein the insulin sensitizer is a compound of the formula [IV] :



5 wherein R represents a hydrocarbon group or a heterocyclic group, each of which may be substituted; Y represents a group of the formula : -CO-, -CH(OH)- or -NR<sup>3</sup>- wherein R<sup>3</sup> represents an alkyl group that may be substituted; m is 0  
10 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents O or S; R<sup>1</sup> represents hydrogen atom or an alkyl group; ring E may have further  
15 1 to 4 substituents, which may form a ring in combination with R<sup>1</sup>; L and M respectively represent hydrogen atom or may be combined with each other to form a chemical bond, or a salt thereof.

3. A pharmaceutical composition according to claim 2,  
20 wherein the compound of the formula [IV] or a salt thereof is pioglitazone or its salt.

4. A pharmaceutical composition according to claim 2,  
wherein the compound of the formula [IV] or a salt thereof  
25 is rosiglitazone or its salt.

5. A pharmaceutical composition according to claim 1, which comprises pioglitazone or its hydrochloride in combination with 2-[3-(7-carboxymethoxyindol-3-yl)-  
30 (2R)-2-propylamino]-(1R)-1-(3-chlorophenyl)ethanol.

6. A pharmaceutical composition according to claim 1, which comprises rosiglitazone or its maleate in combination with 2-[3-(7-carboxymethoxyindol-3-yl)-(2R)-2-propylamino]-(1R)-1-(3-chlorophenyl)ethanol.

5

7. A pharmaceutical composition according to claim 1, which is for preventing or treating diabetes.

8. A pharmaceutical composition according to claim 7, wherein the diabetes is noninsulin-dependent diabetes mellitus.

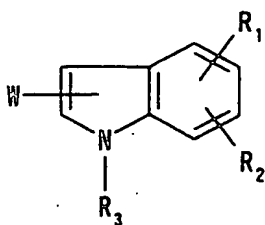
9. A pharmaceutical composition according to claim 1, which is for preventing or treating impaired glucose tolerance, hyperlipidemia, hyperinsulinemia, obesity, hyperphagia, hypertension, cardiovascular diseases, polycystic ovary syndrome, gestational diabetes, pancreatitis, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis, inflammatory bowel diseases, syndrome X, visceral fat obesity syndrome or diabetic complications.

10. A pharmaceutical composition according to claim 9, wherein the diabetic complications are retinopathy, nephropathy, neuropathy, macroangiopathy, diabetic hyperosmolar coma, infectious disease, diabetic osteoporosis, diabetic gangrene, xerostomia, lowered sense of hearing, myocardial infarction, angina pectoris, cerebrovascular disease or peripheral circulatory disturbance.

11. A pharmaceutical composition for inhibiting body weight increase after stopping a smoking habit, which comprises at least one member selected from the group consisting of

1) a compound of the formula [I] :





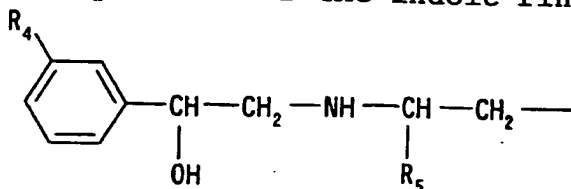
- wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,
- 5 (a) a group of the formula :  $-Xa-Ra$   
 wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;
- (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$
- 15 wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,
- (c) a group of the formula :  $-O(CH_2)_r-Rc$
- 20 wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$   
 wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,
- 25 (d) a group of the formula :  $-Ya-(CH_2)_s-Rd$   
 wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,
- $R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above
- 30 (b) or (c), or combines with  $R_1$  to form the above methylenedioxy group, said methylenedioxy group being

optionally substituted by carboxyl group or a lower alkoxycarbonyl group,

R<sub>3</sub> represents hydrogen atom or a lower alkyl group,

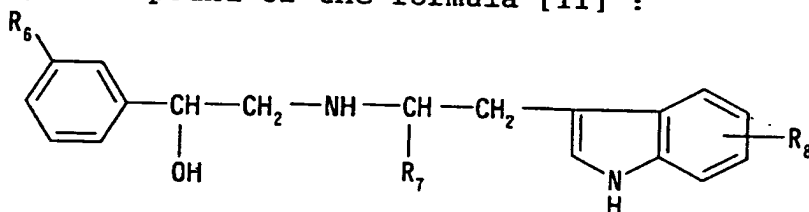
W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:

5 or 3-position of the indole ring in the formula [I]:



wherein R<sub>1</sub> represents a halogen atom or a halogeno lower alkyl group, R<sub>2</sub> represents a lower alkyl group, or a salt thereof;

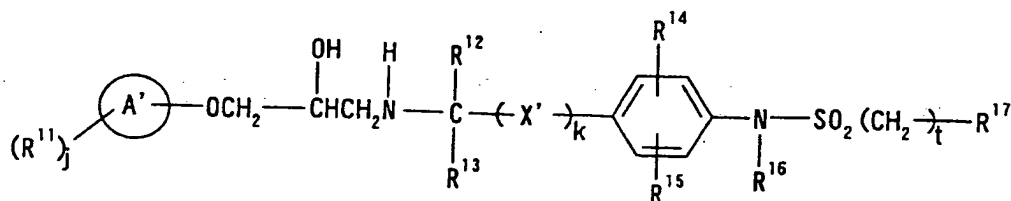
10 2) a compound of the formula [II] :



wherein R<sub>6</sub> represents a halogen atom or a halogeno lower alkyl group, R<sub>7</sub> represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group, R<sub>8</sub> represents

15 hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



wherein j represents an integer of 0 to 7,

20 k represents 0 or 1.

t represents an integer of 0 to 3,

ring A' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3</sub>-

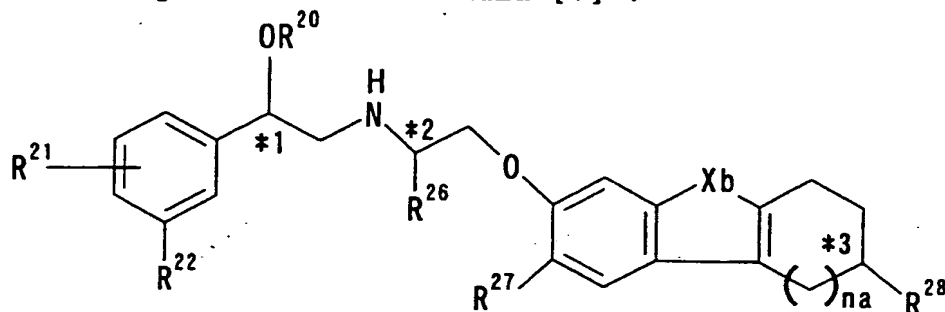
25 cycloalkyl ring; benzene ring condensed with a 5- or 6-

- membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 5  $R^{11}$  represents hydroxy, oxo, halogen, cyano, nitro,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $SO_2R^{19}$ ,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $NR^{18}SO_2R^{19}$ ,  $NR^{18}CO_2R^{18}$ ; or a  $C_{1-6}$  alkyl group substituted by hydroxy, nitro, halogen, cyano,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $SO_2R^{19}$ ,  $NR^{18}SO_2R^{19}$  or  $NR^{18}CO_2R^{18}$ ;
- 10 or  $R^{11}$  represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;  $R^{12}$  and  $R^{13}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, or  $C_{1-6}$  alkyl substituted by hydroxy,  $C_{1-6}$  alkoxy or halogen;  $X'$  represents  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH=CH-$  or  $-CH_2O-$ ;
- 15  $R^{14}$  and  $R^{15}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, halogen,  $NHR^{18}$ ,  $OR^{18}$ ,  $SO_2R^{19}$  or  $NHSO_2R^{19}$ ;
- 20  $R^{16}$  represents hydrogen atom or  $C_{1-6}$  alkyl;  $R^{17}$  represents  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl or  $-B'-(R^{11})_j$ , wherein  $R^{11}$  and  $j$  have the same meanings as above; ring  $B'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $C_{3-8}$  cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 25 30  $R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$  alkyl substituted by hydroxy, halogen,  $CO_2H$ ,  $C_{1-6}$

alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same meaning as above, or a salt thereof;

- 5 4) a compound of the formula [V] :



wherein R<sup>20</sup> represents hydrogen atom or methyl group,

R<sup>21</sup> represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,

- 10 R<sup>22</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>23</sup>, SO<sub>2</sub>NR<sup>24</sup>R<sup>24'</sup> or nitro group,

R<sup>23</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>25</sup>, formyl group or CONHR<sup>26</sup>,

R<sup>25</sup> represents a lower alkyl group, benzyl group or NR<sup>24</sup>R<sup>24'</sup>,

- 15 R<sup>24</sup> and R<sup>24'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

R<sup>26</sup> represents hydrogen atom or a lower alkyl group,

R<sup>26</sup> represents hydrogen atom or a lower alkyl group, na is 1 or 2,

- 20 Xb represents secondary nitrogen atom, O or S,

one of R<sup>27</sup> or R<sup>28</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 1,

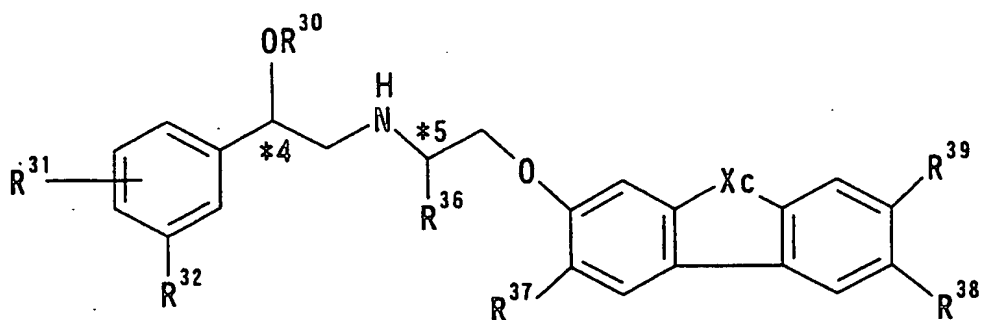
R<sup>28</sup> is hydrogen atom, and R<sup>27</sup> is hydrogen atom, amino group,

- 25 acetylamino group or hydroxy group, when na is 2,

\*1 represents an asymmetric carbon atom,

\*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof; and

- 30 5) a compound of the formula [VI] :



wherein  $R^{30}$  represents hydrogen atom or methyl group,

$R^{21}$  represents hydrogen atom, a halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,

5  $R^{32}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  $SO_2NR^{34}R^{34'}$  or nitro group,

$R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl group or  $CONHR^{36'}$ ,

$R^{35}$  represents a lower alkyl group, benzyl group or  $NR^{34}R^{34'}$ ,

10  $R^{34}$  and  $R^{34'}$  are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

$R^{36'}$  represents hydrogen atom or a lower alkyl group,

$R^{36}$  represents hydrogen atom or a lower alkyl group,

15  $Xc$  represents secondary nitrogen atom, O, S or methylene group,

$R^{39}$  is hydrogen atom, one of  $R^{37}$  or  $R^{38}$  is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when  $Xc$  is secondary nitrogen atom, O or S,

20  $R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when  $Xc$  is methylene group,

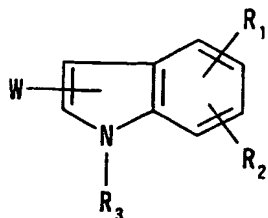
\*4 represents an asymmetric carbon atom,

\*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower

25 alkyl group, or a salt thereof.

12. A pharmaceutical composition for inhibiting body weight increase after stopping alimentary therapy, which comprises at least one member selected from the group  
30 consisting of

1) a compound of the formula [I] :

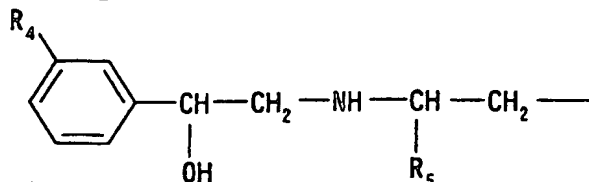


- wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,
- (a) a group of the formula :  $-Xa-Ra$   
 wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;
- (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$   
 wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,
- (c) a group of the formula :  $-O(CH_2)_r-Rc$   
 wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$   
 wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,
- (d) a group of the formula :  $-Ya-(CH_2)_s-Rd$   
 wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,  
 $R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above (b) or (c), or combines with  $R_1$  to form the above

methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

$R_3$  represents hydrogen atom or a lower alkyl group,

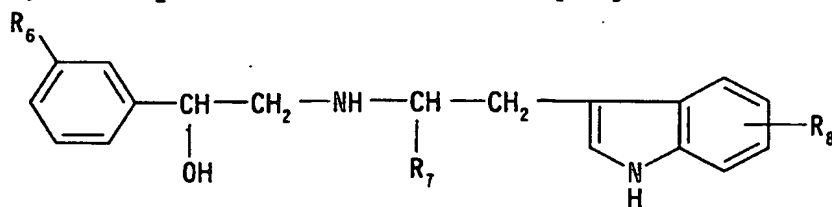
- 5 W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;

10

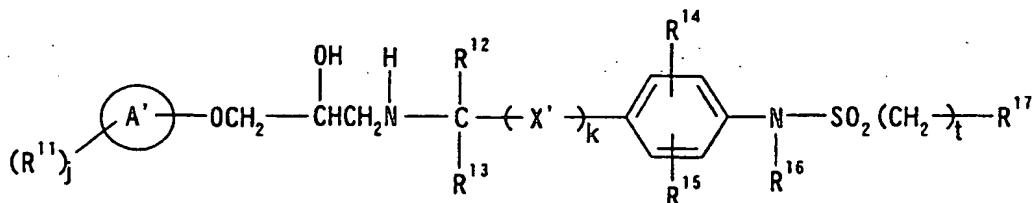
2) a compound of the formula [II] :



wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

15

3) a compound of the formula [III] :



20 wherein  $j$  represents an integer of 0 to 7,

$k$  represents 0 or 1,

$t$  represents an integer of 0 to 3,

ring  $A'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms

25 selected from O, S and N; benzene ring condensed with  $C_{3-8}$

- cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 5  $R^{11}$  represents hydroxy, oxo, halogen, cyano, nitro,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $SO_2R^{19}$ ,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $NR^{18}SO_2R^{19}$ ,  $NR^{18}CO_2R^{18}$ ; or a  $C_{1-6}$  alkyl group substituted by hydroxy, nitro, halogen, cyano,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $SO_2R^{19}$ ,  $NR^{18}SO_2R^{19}$  or  $NR^{18}CO_2R^{18}$ ;
- 10 or  $R^{11}$  represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;  $R^{12}$  and  $R^{13}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, or  $C_{1-6}$  alkyl substituted by hydroxy,  $C_{1-6}$  alkoxy or halogen;  $X'$  represents  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH=CH-$  or  $-CH_2O-$ ;
- 20  $R^{14}$  and  $R^{15}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, halogen,  $NHR^{18}$ ,  $OR^{18}$ ,  $SO_2R^{19}$  or  $NHSO_2R^{19}$ ;  $R^{16}$  represents hydrogen atom or  $C_{1-6}$  alkyl;  $R^{17}$  represents  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl or  $-B'-(R^{11})_j$ , wherein  $R^{11}$  and  $j$  have the same meanings as above;
- 25 ring  $B'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $C_{3-8}$  cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 30  $R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$
- 35

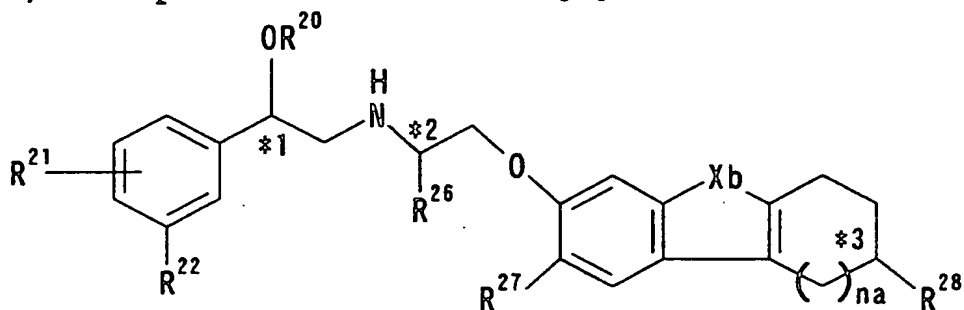


alkyl substituted by hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same

5 meaning as above, or a salt thereof;

4) a compound of the formula [V] :



wherein R<sup>20</sup> represents hydrogen atom or methyl group,

R<sup>21</sup> represents hydrogen atom, halogen atom, hydroxy group,

10 benzyloxy group, amino group or hydroxymethyl group,

R<sup>22</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>23</sup>, SO<sub>2</sub>NR<sup>24</sup>R<sup>24'</sup> or nitro group,

R<sup>23</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>25</sup>, formyl group or CONHR<sup>26'</sup>,

15 R<sup>25</sup> represents a lower alkyl group, benzyl group or NR<sup>24</sup>R<sup>24'</sup>,

R<sup>24</sup> and R<sup>24'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

R<sup>26'</sup> represents hydrogen atom or a lower alkyl group,

R<sup>26</sup> represents hydrogen atom or a lower alkyl group,

20 na is 1 or 2,

X<sub>b</sub> represents secondary nitrogen atom, O or S,

one of R<sup>27</sup> or R<sup>28</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetyl amino group or hydroxy group, when na is 1,

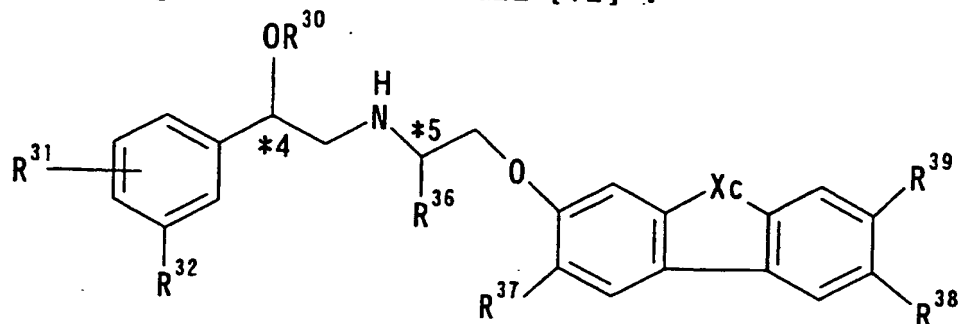
25 R<sup>28</sup> is hydrogen atom, and R<sup>27</sup> is hydrogen atom, amino group, acetyl amino group or hydroxy group, when na is 2,

\*1 represents an asymmetric carbon atom,

\*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof;

30 and

5) a compound of the formula [VI] :

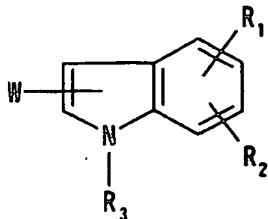


- wherein R<sup>30</sup> represents hydrogen atom or methyl group,  
 R<sup>31</sup> represents hydrogen atom, a halogen atom, hydroxy group,  
 5 benzyloxy group, amino group or hydroxymethyl group,  
 R<sup>32</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>33</sup>,  
 SO<sub>2</sub>NR<sup>34</sup>R<sup>34'</sup> or nitro group,  
 R<sup>33</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>35</sup>, formyl  
 group or CONHR<sup>36</sup>,  
 10 R<sup>35</sup> represents a lower alkyl group, benzyl group or NR<sup>34</sup>R<sup>34'</sup>,  
 R<sup>34</sup> and R<sup>34'</sup> are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,  
 R<sup>36</sup> represents hydrogen atom or a lower alkyl group,  
 R<sup>36</sup> represents hydrogen atom or a lower alkyl group,  
 15 Xc represents secondary nitrogen atom, O, S or methylene  
 group,  
 R<sup>39</sup> is hydrogen atom, one of R<sup>37</sup> or R<sup>38</sup> is hydrogen atom, and  
 the other is hydrogen atom, amino group, acetylamino group  
 or hydroxy group, when Xc is secondary nitrogen atom, O or  
 20 S,  
 R<sup>37</sup> and R<sup>38</sup> are both hydrogen atom, and R<sup>39</sup> is hydrogen atom,  
 amino group, acetylamino group or hydroxy group, when Xc  
 is methylene group,  
 \*4 represents an asymmetric carbon atom,  
 25 \*5 represents an asymmetric carbon atom when R<sup>36</sup> is a lower  
 alkyl group, or a salt thereof.

13. A method for preventing or treating diabetes in a  
 mammal in need thereof, which comprises administering to  
 30 said mammal an effective amount of an insulin sensitizer

in combination with at least one member selected from the group consisting of

1) a compound of the formula [I] :



- 5 wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form  
 10 methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

(a) a group of the formula :  $-Xa-Ra$

- wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower  
 15 alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;

(b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

- wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower  
 20 alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,

(c) a group of the formula :  $-O(CH_2)_r-Rc$

- wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl  
 25 group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$   
 wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

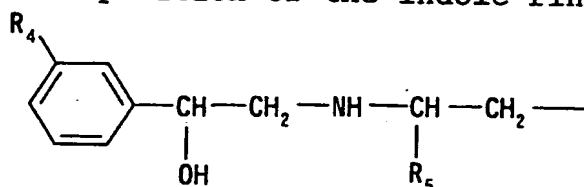
(d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

- wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,  
 30  $R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl

- group, a lower alkoxy group, or the same group as the above (b) or (c), or combines with  $R_1$  to form the above methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

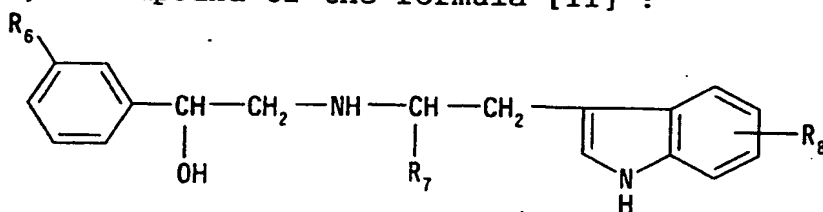
$R_3$  represents hydrogen atom or a lower alkyl group,

$W$  represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



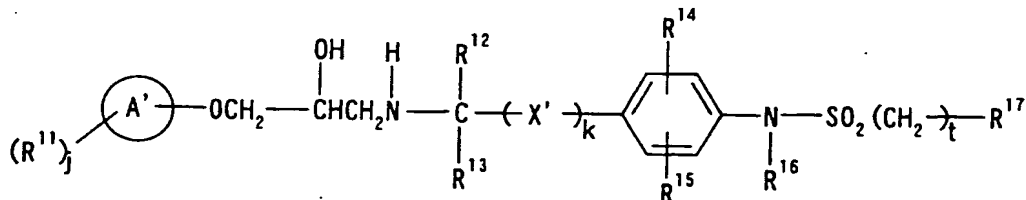
- 10 wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;

2) a compound of the formula [II] :



- 15 wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

- 20 3) a compound of the formula [III] :



wherein  $j$  represents an integer of 0 to 7,

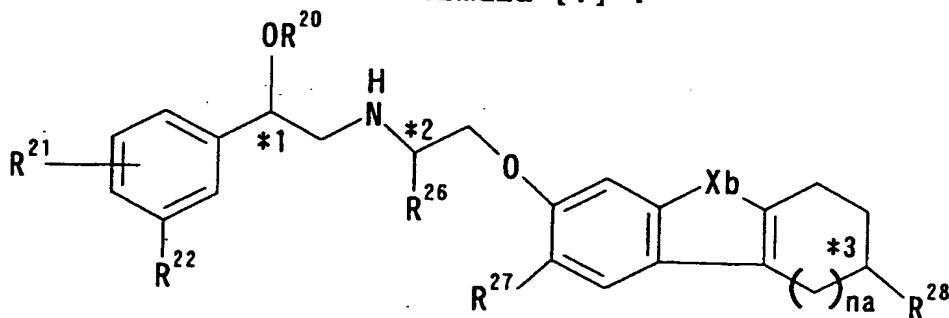
$k$  represents 0 or 1,

$t$  represents an integer of 0 to 3,

- 25 ring  $A'$  represents benzene ring; naphthalene ring; a 5- or

- 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 10 R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;
- 15 or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N; R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;
- 20 X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;
- R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;
- R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;
- 25 R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub>, wherein R<sup>11</sup> and j have the same meanings as above;
- ring B' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 30
- 35

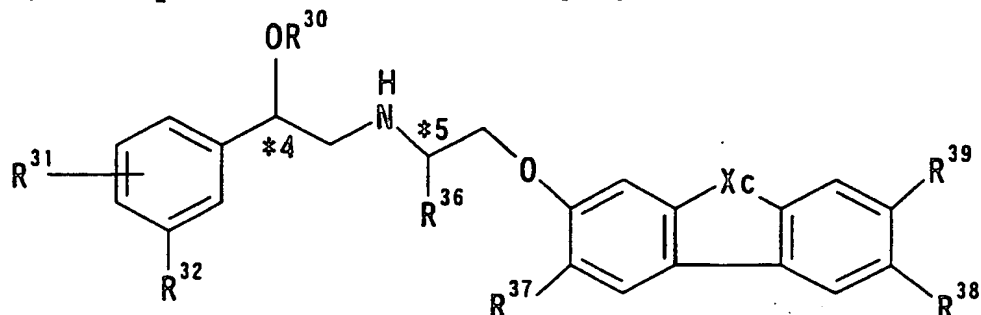
- $R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$  alkyl substituted by hydroxy, halogen,  $CO_2H$ ,  $C_{1-6}$  alkoxy-carbonyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkoxy, or phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;
- $R^{19}$  represents  $R^{18}$ ,  $NHR^{18}$  or  $NR^{18}$  wherein  $R^{18}$  has the same meaning as above, or a salt thereof;
- 4) a compound of the formula [V] :



- wherein  $R^{20}$  represents hydrogen atom or methyl group,  $R^{21}$  represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,  $R^{22}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{23}$ ,  $SO_2NR^{24}R^{24'}$  or nitro group,
- $R^{23}$  represents hydrogen atom, methyl group,  $SO_2NR^{25}$ , formyl group or  $CONHR^{26'}$ ,
- $R^{25}$  represents a lower alkyl group, benzyl group or  $NR^{24}R^{24'}$ ,  $R^{24}$  and  $R^{24'}$  are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,
- $R^{26'}$  represents hydrogen atom or a lower alkyl group,  $R^{26}$  represents hydrogen atom or a lower alkyl group, na is 1 or 2,
- $Xb$  represents secondary nitrogen atom, O or S, one of  $R^{27}$  or  $R^{28}$  is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 1,
- $R^{28}$  is hydrogen atom, and  $R^{27}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 2,
- \*1 represents an asymmetric carbon atom,
- \*2 and \*3 represent an asymmetric carbon atom when  $R^{26}$  and

$R^{28}$  are respectively not hydrogen atom, or a salt thereof;  
and

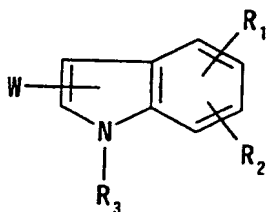
5) a compound of the formula [VI] :



- 5 wherein  $R^{30}$  represents hydrogen atom or methyl group,  
 $R^{21}$  represents hydrogen atom, a halogen atom, hydroxy group,  
benzyloxy group, amino group or hydroxymethyl group,  
 $R^{32}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  
 $SO_2NR^{34}R^{34'}$  or nitro group,  
10  $R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl  
group or  $CONHR^{36'}$ ,  
 $R^{35}$  represents a lower alkyl group, benzyl group or  $NR^{34}R^{34'}$ ,  
 $R^{34}$  and  $R^{34'}$  are the same or different, and represent hydrogen  
atom, a lower alkyl group or benzyl group,  
15  $R^{36'}$  represents hydrogen atom or a lower alkyl group,  
 $R^{36}$  represents hydrogen atom or a lower alkyl group,  
 $Xc$  represents secondary nitrogen atom, O, S or methylene  
group,  
 $R^{39}$  is hydrogen atom, one of  $R^{37}$  or  $R^{38}$  is hydrogen atom, and  
20 the other is hydrogen atom, amino group, acetylamino group  
or hydroxy group, when  $Xc$  is secondary nitrogen atom, O or  
S,  
 $R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom,  
amino group, acetylamino group or hydroxy group, when  $Xc$   
25 is methylene group,  
\*4 represents an asymmetric carbon atom,  
\*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower  
alkyl group, or a salt thereof.

30 14. A method for preventing or treating impaired glucose

- tolerance, hyperlipidemia, hyperinsulinemia, obesity, hyperphagia, hypertension, cardiovascular diseases, polycystic ovary syndrome, gestational diabetes, pancreatitis, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis, inflammatory bowel diseases, syndrome X, visceral fat obesity syndrome or diabetic complications, in a mammal in need thereof, which comprises administering to said mammal an effective amount of an insulin sensitizer in combination with at least one member selected from the group consisting of
- 1) a compound of the formula [I] :



- wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,
- (a) a group of the formula :  $-Xa-Ra$   
wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;
  - (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$   
wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,
  - (c) a group of the formula :  $-O(CH_2)_r-Rc$   
wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl



group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$

wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

(d) a group of the formula :  $-Ya-(CH_2)_s-R_d$

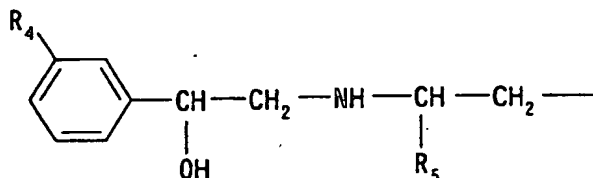
5 wherein  $Ya$  is  $NH$  or  $S$ ,  $R_d$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,

$R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above

10 (b) or (c), or combines with  $R_1$  to form the above methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

$R_3$  represents hydrogen atom or a lower alkyl group,

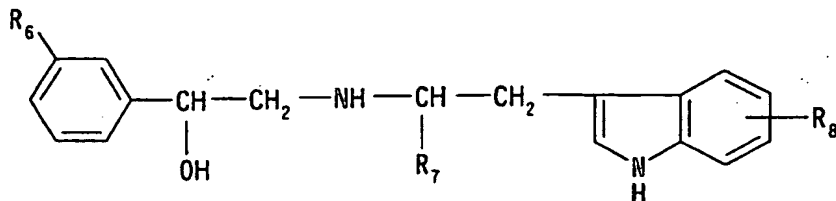
15  $W$  represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt

20 thereof;

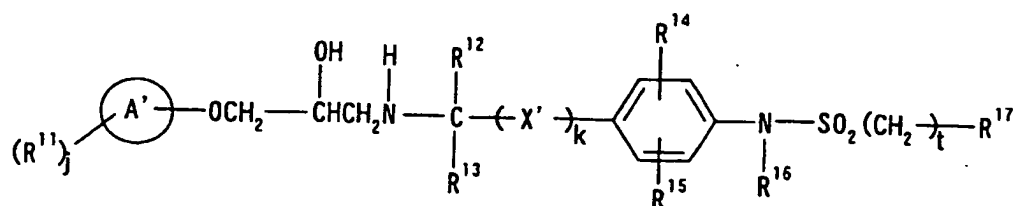
2) a compound of the formula [II] :



wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl

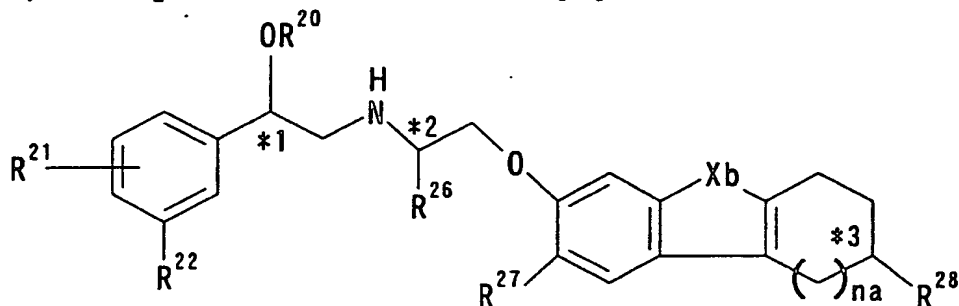
25 group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



- wherein j represents an integer of 0 to 7,  
 k represents 0 or 1,  
 t represents an integer of 0 to 3,
- 5 ring A' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms
  - 10 selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
  - 15 R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;
  - 20 or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N; R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;
  - 25 X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;
  - R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;
  - R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;
  - 30 R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub> wherein R<sup>11</sup> and j have the same meanings as above; ring B' represents benzene ring; naphthalene ring; a 5- or

- 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 10 R<sup>18</sup> represents hydrogen atom; C<sub>1-10</sub> alkyl; C<sub>3-8</sub> cycloalkyl; phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; C<sub>1-10</sub> alkyl substituted by hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;
- 15 R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same meaning as above, or a salt thereof;
- 4) a compound of the formula [V] :



- wherein R<sup>20</sup> represents hydrogen atom or methyl group,
- 20 R<sup>21</sup> represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,
- R<sup>22</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>23</sup>, SO<sub>2</sub>NR<sup>24</sup>R<sup>24'</sup> or nitro group,
- R<sup>23</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>25</sup>, formyl group or CONHR<sup>26</sup>,
- 25 R<sup>25</sup> represents a lower alkyl group, benzyl group or NR<sup>24</sup>R<sup>24'</sup>,
- R<sup>24</sup> and R<sup>24'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,
- R<sup>26</sup> represents hydrogen atom or a lower alkyl group,
- 30 R<sup>26</sup> represents hydrogen atom or a lower alkyl group,

na is 1 or 2,

Xb represents secondary nitrogen atom, O or S,

one of R<sup>27</sup> or R<sup>28</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when

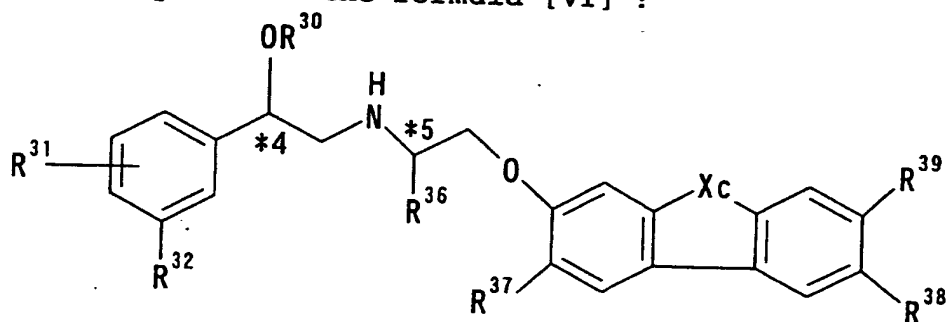
5 na is 1,

R<sup>28</sup> is hydrogen atom, and R<sup>27</sup> is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 2,

\*1 represents an asymmetric carbon atom,

\*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof; and

10 5) a compound of the formula [VI] :



wherein R<sup>30</sup> represents hydrogen atom or methyl group,

15 R<sup>31</sup> represents hydrogen atom, a halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,

R<sup>32</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>33</sup>, SO<sub>2</sub>NR<sup>34</sup>R<sup>34'</sup> or nitro group,

20 R<sup>33</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>35</sup>, formyl group or CONHR<sup>36</sup>,

R<sup>35</sup> represents a lower alkyl group, benzyl group or NR<sup>34</sup>R<sup>34'</sup>,

R<sup>34</sup> and R<sup>34'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

25 R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

Xc represents secondary nitrogen atom, O, S or methylene group,

30 R<sup>39</sup> is hydrogen atom, one of R<sup>37</sup> or R<sup>38</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is secondary nitrogen atom, O or

S,

$R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is methylene group,

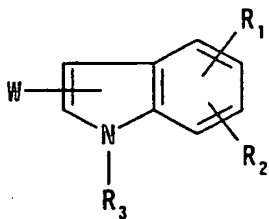
5 \*4 represents an asymmetric carbon atom,

\*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower alkyl group, or a salt thereof.

10 15. A method according to claim 14, wherein the diabetic complications are retinopathy, nephropathy, neuropathy, macroangiopathy, diabetic hyperosmolar coma, infectious disease, diabetic osteoporosis, diabetic gangrene, xerostomia, lowered sense of hearing, myocardial infarction, angina pectoris, cerebrovascular disease or  
15 peripheral circulatory disturbance.

16. A method for inhibiting body weight increase after stopping a smoking habit in human in need thereof, which comprises administering to said human an effective amount  
20 of at least one member selected from the group consisting of

1) a compound of the formula [I] :

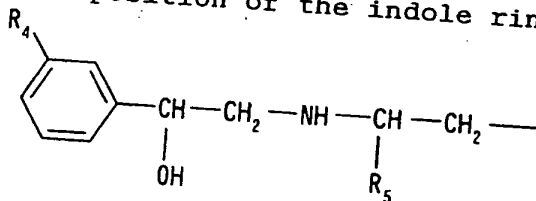


wherein  $R_1$  represents a lower alkyl group optionally  
25 substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being  
30 optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

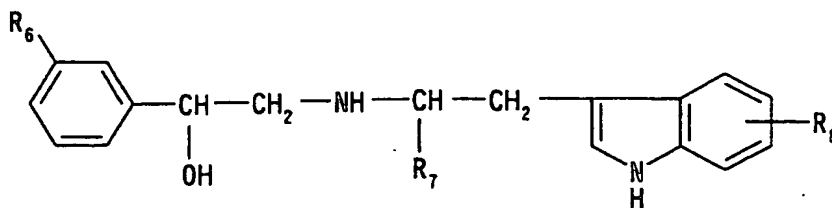
(a) a group of the formula : -Xa-Ra

wherein Xa is O, S or NH, Ra is hydrogen atom or a lower alkyl group, provided that Ra is a lower alkyl group when Xa is S;

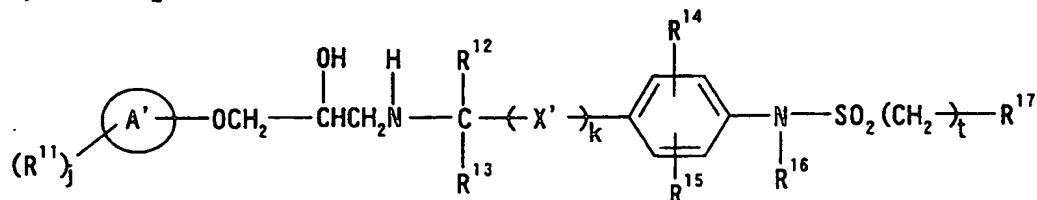
- (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qR_{bb}$   
 5 wherein Rb is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group, Rbb is a lower alkoxy carbonyl group or carboxyl group, p is an integer of 0 to 3, q is 0 or 1,  
 (c) a group of the formula :  $-O(CH_2)_r-Rc$   
 10 wherein Rc is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$   
 wherein  $R_A$  is hydrogen atom or a lower alkyl group, r is an integer of 1 to 4,  
 (d) a group of the formula :  $-Ya-(CH_2)_s-Rd$   
 15 wherein Ya is NH or S, Rd is carboxyl group or a lower alkoxy carbonyl group, s is an integer of 1 to 4,  
 $R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above  
 20 (b) or (c), or combines with  $R_1$  to form the above methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,  
 25  $R_3$  represents hydrogen atom or a lower alkyl group,  
 W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



- wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;  
 30 2) a compound of the formula [II] :

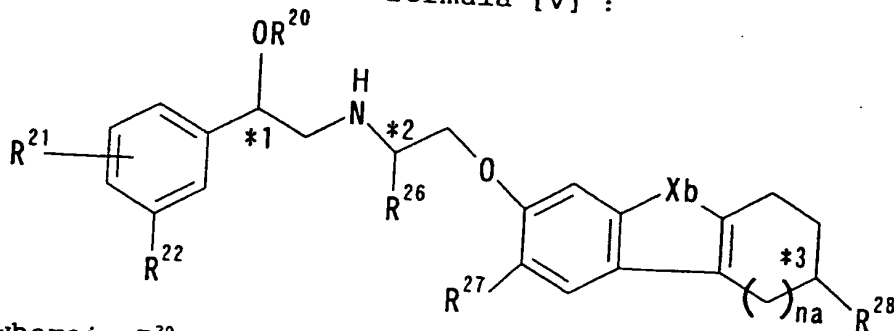


- wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;
- 3) a compound of the formula [III] :



- wherein  $j$  represents an integer of 0 to 7,
- $k$  represents 0 or 1,
- $t$  represents an integer of 0 to 3,
- ring  $A'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $C_{3-8}$  cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- $R^{11}$  represents hydroxy, oxo, halogen, cyano, nitro,  $NR^{18}R^{19}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $SO_2R^{19}$ ,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $NR^{18}SO_2R^{19}$ ,  $NR^{18}CO_2R^{18}$ ; or a  $C_{1-6}$  alkyl group substituted by hydroxy, nitro, halogen, cyano,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $SO_2R^{19}$ ,  $NR^{18}SO_2R^{19}$  or  $NR^{18}CO_2R^{18}$ ;

- or  $R^{11}$  represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;  $R^{12}$  and  $R^{13}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, or  $C_{1-6}$  alkyl substituted by hydroxy,  $C_{1-6}$  alkoxy or halogen;
- 5  $X'$  represents  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH=CH-$  or  $-CH_2O-$ ;
- $R^{14}$  and  $R^{15}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, halogen,  $NHR^{18}$ ,  $OR^{18}$ ,  $SO_2R^{19}$  or  $NHSO_2R^{19}$ ;
- $R^{16}$  represents hydrogen atom or  $C_{1-6}$  alkyl;
- $R^{17}$  represents  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl or  $-B'-(R^{11})_j$ ,
- 10 wherein  $R^{11}$  and  $j$  have the same meanings as above;
- ring  $B'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $C_{3-8}$  cycloalkyl ring; benzene ring condensed with a 5- or 6-
- 15 membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and
- 20 N;
- $R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$  alkyl substituted by hydroxy, halogen,  $CO_2H$ ,  $C_{1-6}$  alkoxy-carbonyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkoxy, or phenyl
- 25 substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;
- $R^{19}$  represents  $R^{18}$ ,  $NHR^{18}$  or  $NR^{18}$  wherein  $R^{18}$  has the same meaning as above, or a salt thereof;
- 4) a compound of the formula [V] :



- 30 wherein  $R^{20}$  represents hydrogen atom or methyl group,



$R^{21}$  represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,  
 $R^{22}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{23}$ ,  $SO_2NR^{24}R^{24'}$  or nitro group,

5  $R^{23}$  represents hydrogen atom, methyl group,  $SO_2NR^{25}$ , formyl group or  $CONHR^{26}$ ,

$R^{25}$  represents a lower alkyl group, benzyl group or  $NR^{24}R^{24'}$ ,  
 $R^{24}$  and  $R^{24'}$  are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

10  $R^{26}$  represents hydrogen atom or a lower alkyl group,

$R^{26}$  represents hydrogen atom or a lower alkyl group,  
na is 1 or 2,

Xb represents secondary nitrogen atom, O or S,

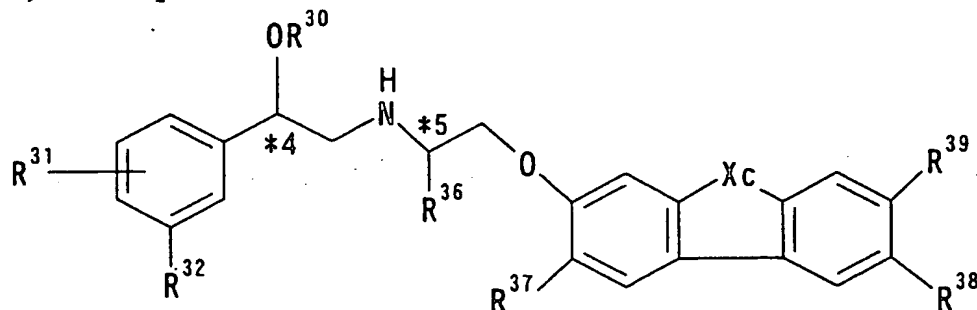
one of  $R^{27}$  or  $R^{28}$  is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when  
15 na is 1,

$R^{28}$  is hydrogen atom, and  $R^{27}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 2,

\*1 represents an asymmetric carbon atom,

20 \*2 and \*3 represent an asymmetric carbon atom when  $R^{26}$  and  $R^{28}$  are respectively not hydrogen atom, or a salt thereof;  
and

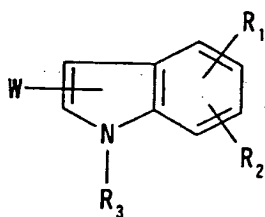
5) a compound of the formula [VI] :



25 wherein  $R^{30}$  represents hydrogen atom or methyl group,  
 $R^{21}$  represents hydrogen atom, a halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,  
 $R^{32}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  $SO_2NR^{34}R^{34'}$  or nitro group,

30  $R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl

- group or  $\text{CONHR}^{36'}$ ,  
 $\text{R}^{35}$  represents a lower alkyl group, benzyl group or  $\text{NR}^{34'}\text{R}^{34''}$ ,  
 $\text{R}^{34}$  and  $\text{R}^{34'}$  are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,
- 5  $\text{R}^{36'}$  represents hydrogen atom or a lower alkyl group,  
 $\text{R}^{36}$  represents hydrogen atom or a lower alkyl group,  
 $\text{Xc}$  represents secondary nitrogen atom, O, S or methylene group,
- 10  $\text{R}^{39}$  is hydrogen atom, one of  $\text{R}^{37}$  or  $\text{R}^{38}$  is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when  $\text{Xc}$  is secondary nitrogen atom, O or S,  
 $\text{R}^{37}$  and  $\text{R}^{38}$  are both hydrogen atom, and  $\text{R}^{39}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when  $\text{Xc}$  is methylene group,
- 15  $\ast 4$  represents an asymmetric carbon atom,  
 $\ast 5$  represents an asymmetric carbon atom when  $\text{R}^{36}$  is a lower alkyl group, or a salt thereof.
- 20 17. A method for inhibiting body weight increase after stopping alimentary therapy in human in need thereof, which comprises administering to said human an effective amount of at least one member selected from the group consisting of
- 25 1) a compound of the formula [I] :



- wherein  $\text{R}_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $\text{R}_2$  to form methylenedioxy group, said methylenedioxy group being
- 30

optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

(a) a group of the formula :  $-Xa-Ra$

wherein Xa is O, S or NH, Ra is hydrogen atom or a lower alkyl group, provided that Ra is a lower alkyl group when Xa is S;

(b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

wherein Rb is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group, Rbb is a lower alkoxy carbonyl group or carboxyl group, p is an integer of 0 to 3, q is 0 or 1,

(c) a group of the formula :  $-O(CH_2)_r-Rc$

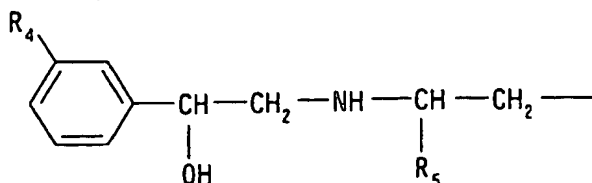
wherein Rc is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$  wherein  $R_A$  is hydrogen atom or a lower alkyl group, r is an integer of 1 to 4,

(d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

wherein Ya is NH or S, Rd is carboxyl group or a lower alkoxy carbonyl group, s is an integer of 1 to 4,  $R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above (b) or (c), or combines with  $R_1$  to form the above methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

$R_3$  represents hydrogen atom or a lower alkyl group,

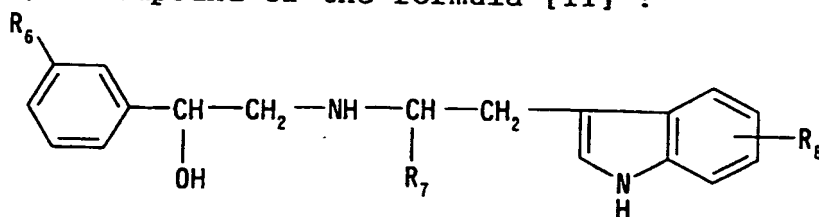
W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt

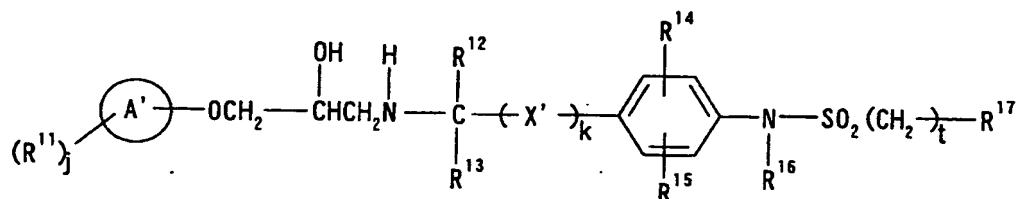
thereof;

2) a compound of the formula [II] :



wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



10

wherein  $j$  represents an integer of 0 to 7,

$k$  represents 0 or 1,

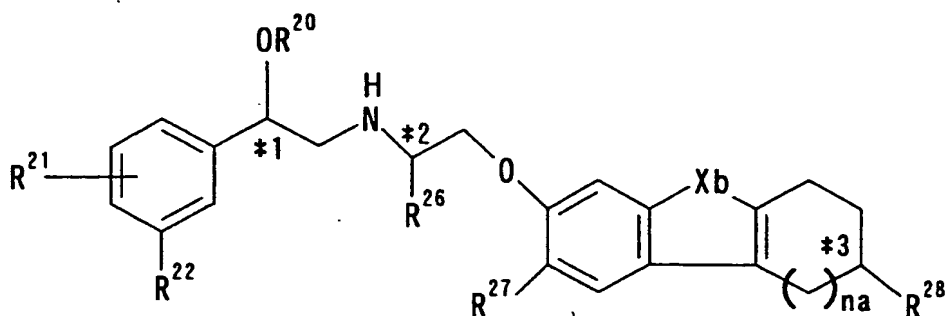
$t$  represents an integer of 0 to 3,

ring  $A'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $\text{C}_{3-6}$  cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;

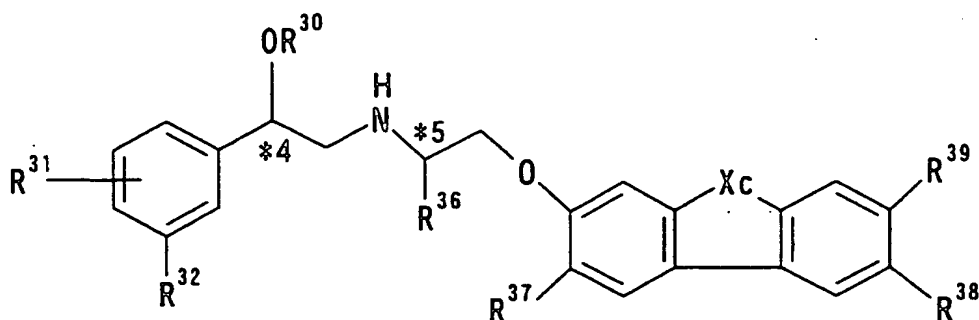
$\text{R}^{11}$  represents hydroxy, oxo, halogen, cyano, nitro,  $\text{NR}^{18}\text{R}^{18}$ ,  $\text{SR}^{18}$ , a halogeno lower alkyl,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{3-6}$  cycloalkyl, phenyl,  $\text{SO}_2\text{R}^{19}$ ,  $\text{NR}^{18}\text{COR}^{19}$ ,  $\text{COR}^{19}$ ,  $\text{NR}^{18}\text{SO}_2\text{R}^{19}$ ,  $\text{NR}^{18}\text{CO}_2\text{R}^{18}$ ; or a  $\text{C}_{1-6}$  alkyl group substituted by hydroxy, nitro, halogen, cyano,  $\text{NR}^{18}\text{R}^{18}$ ,  $\text{SR}^{18}$ , a halogeno lower alkyl,  $\text{C}_{1-6}$

25

- alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;
- or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;
- 5 R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen; X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;
- R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;
- 10 R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl; R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub>, wherein R<sup>11</sup> and j have the same meanings as above; ring B' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms
- 15 selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and
- 20 N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- R<sup>18</sup> represents hydrogen atom; C<sub>1-10</sub> alkyl; C<sub>3-8</sub> cycloalkyl; phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; C<sub>1-10</sub>
- 25 alkyl substituted by hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;
- R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same meaning as above, or a salt thereof;
- 30 4) a compound of the formula [V] :



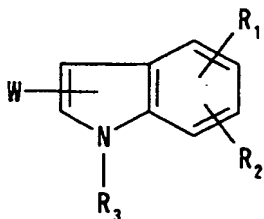
- wherein  $R^{20}$  represents hydrogen atom or methyl group,  
 $R^{21}$  represents hydrogen atom, halogen atom, hydroxy group,  
benzyloxy group, amino group or hydroxymethyl group,  
5  $R^{22}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{23}$ ,  
 $SO_2NR^{24}R^{24'}$  or nitro group,  
 $R^{23}$  represents hydrogen atom, methyl group,  $SO_2NR^{25}$ , formyl  
group or  $CONHR^{26'}$ ,  
 $R^{25}$  represents a lower alkyl group, benzyl group or  $NR^{24}R^{24'}$ ,  
10  $R^{24}$  and  $R^{24'}$  are the same or different, and represent hydrogen  
atom, a lower alkyl group or benzyl group,  
 $R^{26'}$  represents hydrogen atom or a lower alkyl group,  
 $R^{26}$  represents hydrogen atom or a lower alkyl group,  
na is 1 or 2,  
15 Xb represents secondary nitrogen atom, O or S,  
one of  $R^{27}$  or  $R^{28}$  is hydrogen atom, and the other is hydrogen  
atom, amino group, acetylamino group or hydroxy group, when  
na is 1,  
 $R^{28}$  is hydrogen atom, and  $R^{27}$  is hydrogen atom, amino group,  
20 acetylamino group or hydroxy group, when na is 2,  
\*1 represents an asymmetric carbon atom,  
\*2 and \*3 represent an asymmetric carbon atom when  $R^{26}$  and  
 $R^{28}$  are respectively not hydrogen atom, or a salt thereof;  
and  
25 5) a compound of the formula [VI] :



- wherein  $R^{30}$  represents hydrogen atom or methyl group,  
 $R^{21}$  represents hydrogen atom, a halogen atom, hydroxy group,  
 benzyloxy group, amino group or hydroxymethyl group,  
 5  $R^{32}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  
 $SO_2NR^{34}R^{34'}$  or nitro group,  
 $R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl  
 group or  $CONHR^{36'}$ ,  
 $R^{35}$  represents a lower alkyl group, benzyl group or  $NR^{34}R^{34'}$ ,  
 10  $R^{34}$  and  $R^{34'}$  are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,  
 $R^{36'}$  represents hydrogen atom or a lower alkyl group,  
 $R^{36}$  represents hydrogen atom or a lower alkyl group,  
 $Xc$  represents secondary nitrogen atom, O, S or methylene  
 15 group,  
 $R^{39}$  is hydrogen atom, one of  $R^{37}$  or  $R^{38}$  is hydrogen atom, and  
 the other is hydrogen atom, amino group, acetylamino group  
 or hydroxy group, when  $Xc$  is secondary nitrogen atom, O or  
 S,  
 20  $R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom,  
 amino group, acetylamino group or hydroxy group, when  $Xc$   
 is methylene group,  
 $*4$  represents an asymmetric carbon atom,  
 $*5$  represents an asymmetric carbon atom when  $R^{36}$  is a lower  
 25 alkyl group, or a salt thereof.

18. Use of an insulin sensitizer for the manufacture of  
 a pharmaceutical preparation for treating diabetes, which  
 is used in combination with at least one member selected  
 30 from the group consisting of

1) a compound of the formula [I] :



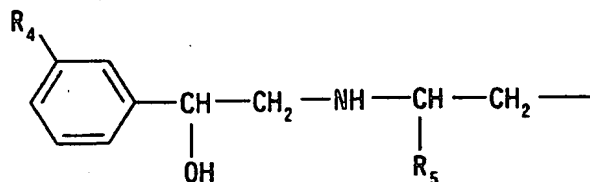
- wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,
- (a) a group of the formula :  $-Xa-Ra$   
 wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;
- (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$   
 wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,
- (c) a group of the formula :  $-O(CH_2)_r-Rc$   
 wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$   
 wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,
- (d) a group of the formula :  $-Ya-(CH_2)_s-Rd$   
 wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,
- $R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above (b) or (c), or combines with  $R_1$  to form the above



methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

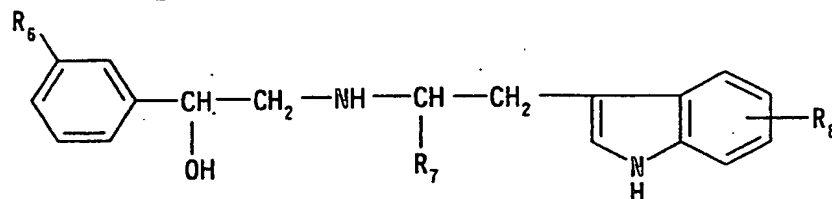
$R_1$  represents hydrogen atom or a lower alkyl group,

- 5 W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



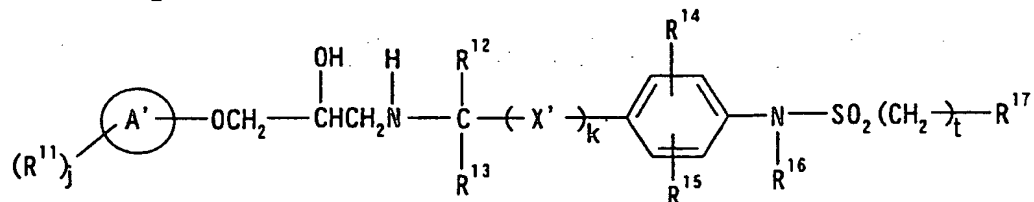
- wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;

2) a compound of the formula [II] :



- wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



- 20 wherein  $j$  represents an integer of 0 to 7,

$k$  represents 0 or 1,

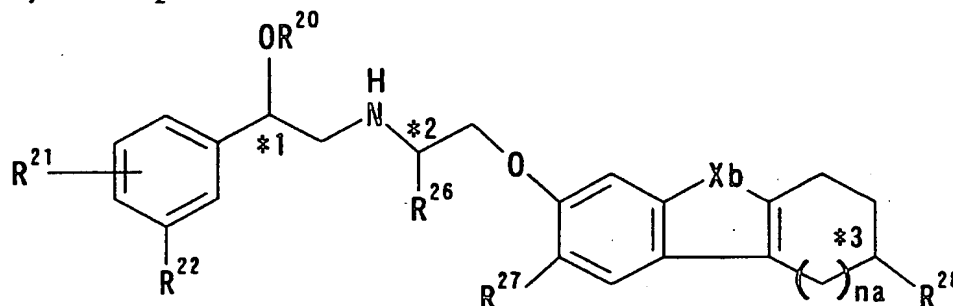
$t$  represents an integer of 0 to 3,

ring  $A'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms

- 25 selected from O, S and N; benzene ring condensed with  $C_{3-8}$

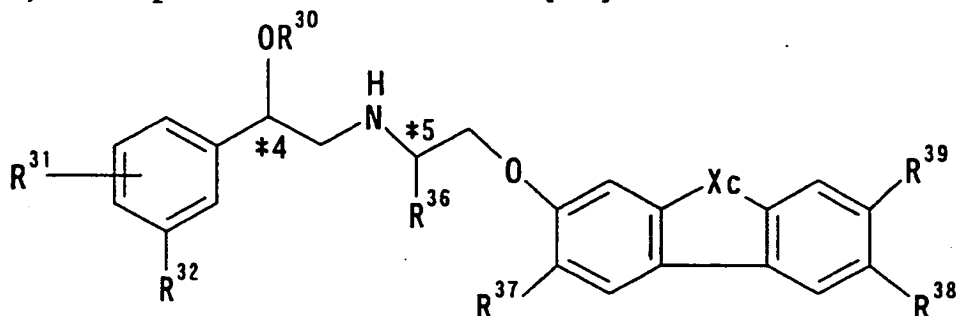
- cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- $R^{11}$  represents hydroxy, oxo, halogen, cyano, nitro,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $SO_2R^{19}$ ,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $NR^{18}SO_2R^{19}$ ,  $NR^{18}CO_2R^{18}$ ; or a  $C_{1-6}$  alkyl group substituted by hydroxy, nitro, halogen, cyano,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $SO_2R^{19}$ ,  $NR^{18}SO_2R^{19}$  or  $NR^{18}CO_2R^{18}$ ;
- or  $R^{11}$  represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;  $R^{12}$  and  $R^{13}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, or  $C_{1-6}$  alkyl substituted by hydroxy,  $C_{1-6}$  alkoxy or halogen;  $X'$  represents  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH=CH-$  or  $-CH_2O-$ ;
- $R^{14}$  and  $R^{15}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, halogen,  $NHR^{18}$ ,  $OR^{18}$ ,  $SO_2R^{19}$  or  $NHSO_2R^{19}$ ;
- $R^{16}$  represents hydrogen atom or  $C_{1-6}$  alkyl;
- $R^{17}$  represents  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl or  $-B'-(R^{11})_j$ , wherein  $R^{11}$  and  $j$  have the same meanings as above;
- ring  $B'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $C_{3-8}$  cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- $R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$

alkyl substituted by hydroxy, halogen,  $\text{CO}_2\text{H}$ ,  $\text{C}_{1-6}$  alkoxy-carbonyl,  $\text{C}_{3-8}$  cycloalkyl,  $\text{C}_{1-6}$  alkoxy, or phenyl substituted by halogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{1-6}$  alkoxy;  
 $\text{R}^{19}$  represents  $\text{R}^{18}$ ,  $\text{NHR}^{18}$  or  $\text{NR}^{18}$  wherein  $\text{R}^{18}$  has the same  
 5 meaning as above, or a salt thereof;  
 4) a compound of the formula [V] :



wherein  $\text{R}^{20}$  represents hydrogen atom or methyl group,  
 $\text{R}^{21}$  represents hydrogen atom, halogen atom, hydroxy group,  
 10 benzyloxy group, amino group or hydroxymethyl group,  
 $\text{R}^{22}$  represents hydrogen atom, hydroxymethyl group,  $\text{NHR}^{23}$ ,  
 $\text{SO}_2\text{NR}^{24}\text{R}^{24'}$  or nitro group,  
 $\text{R}^{23}$  represents hydrogen atom, methyl group,  $\text{SO}_2\text{NR}^{25}$ , formyl  
 group or  $\text{CONHR}^{26'}$ ,  
 15  $\text{R}^{25}$  represents a lower alkyl group, benzyl group or  $\text{NR}^{24}\text{R}^{24'}$ ,  
 $\text{R}^{24}$  and  $\text{R}^{24'}$  are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,  
 $\text{R}^{26'}$  represents hydrogen atom or a lower alkyl group,  
 $\text{R}^{26}$  represents hydrogen atom or a lower alkyl group,  
 20 na is 1 or 2,  
 $\text{Xb}$  represents secondary nitrogen atom, O or S,  
 one of  $\text{R}^{27}$  or  $\text{R}^{28}$  is hydrogen atom, and the other is hydrogen  
 atom, amino group, acetylamino group or hydroxy group, when  
 na is 1,  
 25  $\text{R}^{28}$  is hydrogen atom, and  $\text{R}^{27}$  is hydrogen atom, amino group,  
 acetylamino group or hydroxy group, when na is 2,  
 \*1 represents an asymmetric carbon atom,  
 \*2 and \*3 represent an asymmetric carbon atom when  $\text{R}^{26}$  and  
 $\text{R}^{28}$  are respectively not hydrogen atom, or a salt thereof;  
 30 and

5) a compound of the formula [VI] :



wherein  $R^{30}$  represents hydrogen atom or methyl group,  
 $R^{31}$  represents hydrogen atom, a halogen atom, hydroxy group,  
 5 benzyloxy group, amino group or hydroxymethyl group,  
 $R^{32}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  
 $SO_2NR^{34}R^{34'}$  or nitro group,

$R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl  
 group or  $CONHR^{36}$ ,

10  $R^{35}$  represents a lower alkyl group, benzyl group or  $NR^{34}R^{34'}$ ,  
 $R^{34}$  and  $R^{34'}$  are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,

$R^{36}$  represents hydrogen atom or a lower alkyl group,

$R^{36}$  represents hydrogen atom or a lower alkyl group,

15  $Xc$  represents secondary nitrogen atom, O, S or methylene  
 group,

$R^{39}$  is hydrogen atom, one of  $R^{37}$  or  $R^{38}$  is hydrogen atom, and  
 the other is hydrogen atom, amino group, acetyl amino group  
 or hydroxy group, when  $Xc$  is secondary nitrogen atom, O or

20 S,

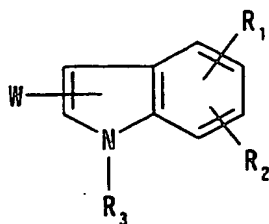
$R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom,  
 amino group, acetyl amino group or hydroxy group, when  $Xc$   
 is methylene group,

\*4 represents an asymmetric carbon atom,

25 \*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower  
 alkyl group, or a salt thereof.

19. Use of at least one member selected from the group  
 consisting of

30 1) a compound of the formula [I] :



wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

(a) a group of the formula :  $-Xa-Ra$

wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;

(b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,

(c) a group of the formula :  $-O(CH_2)_r-Rc$

wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$

wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

(d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,

$R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl

group, a lower alkoxy group, or the same group as the above

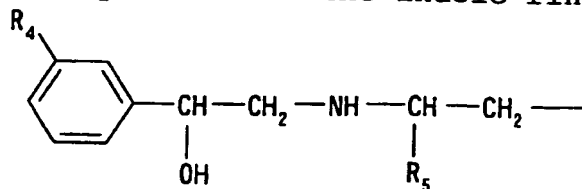
(b) or (c), or combines with  $R_1$  to form the above

methylenedioxy group, said methylenedioxy group being

optionally substituted by carboxyl group or a lower alkoxy carbonyl group.

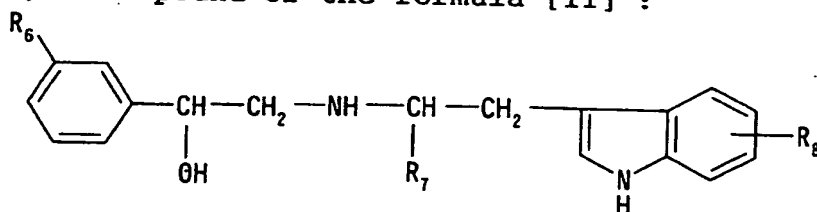
R<sub>3</sub> represents hydrogen atom or a lower alkyl group.

W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



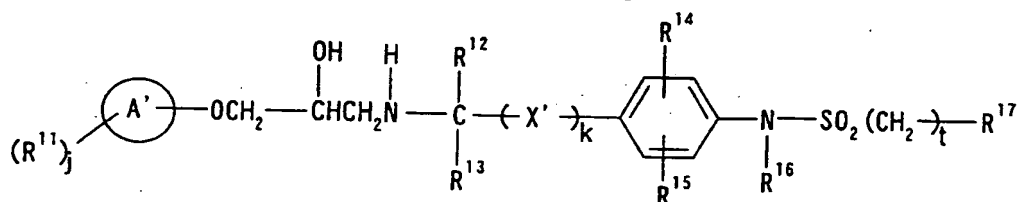
wherein R<sub>4</sub> represents a halogen atom or a halogeno lower alkyl group, R<sub>5</sub> represents a lower alkyl group, or a salt thereof;

2) a compound of the formula [II] :



wherein R<sub>6</sub> represents a halogen atom or a halogeno lower alkyl group, R<sub>7</sub> represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group, R<sub>8</sub> represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



wherein j represents an integer of 0 to 7,

k represents 0 or 1,

t represents an integer of 0 to 3,

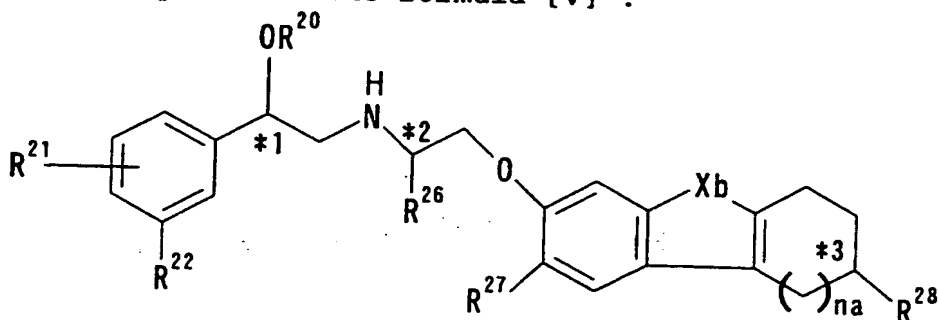
ring A' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub>

cycloalkyl ring; benzene ring condensed with a 5- or 6-

- membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 5  $R^{11}$  represents hydroxy, oxo, halogen, cyano, nitro,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $SO_2R^{19}$ ,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $NR^{18}SO_2R^{19}$ ,  $NR^{18}CO_2R^{18}$ ; or a  $C_{1-6}$  alkyl group substituted by hydroxy, nitro, halogen, cyano,  $NR^{18}R^{18}$ ,  $SR^{18}$ , a halogeno lower alkyl,  $C_{1-6}$  alkoxy,  $C_{3-8}$  cycloalkyl, phenyl,  $NR^{18}COR^{19}$ ,  $COR^{19}$ ,  $SO_2R^{19}$ ,  $NR^{18}SO_2R^{19}$  or  $NR^{18}CO_2R^{18}$ ;
- 10 or  $R^{11}$  represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;  $R^{12}$  and  $R^{13}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, or  $C_{1-6}$  alkyl substituted by hydroxy,  $C_{1-6}$  alkoxy or halogen;  $X'$  represents  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH=CH-$  or  $-CH_2O-$ ;
- 15  $R^{14}$  and  $R^{15}$  represent independently hydrogen atom,  $C_{1-6}$  alkyl, halogen,  $NHR^{18}$ ,  $OR^{18}$ ,  $SO_2R^{19}$  or  $NHSO_2R^{19}$ ;
- 20  $R^{16}$  represents hydrogen atom or  $C_{1-6}$  alkyl;  $R^{17}$  represents  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl or  $-B'-(R^{11})$ , wherein  $R^{11}$  and  $j$  have the same meanings as above; ring  $B'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $C_{3-8}$  cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 25 30 35  $R^{18}$  represents hydrogen atom;  $C_{1-10}$  alkyl;  $C_{3-8}$  cycloalkyl; phenyl substituted by halogen,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy;  $C_{1-10}$  alkyl substituted by hydroxy, halogen,  $CO_2H$ ,  $C_{1-6}$

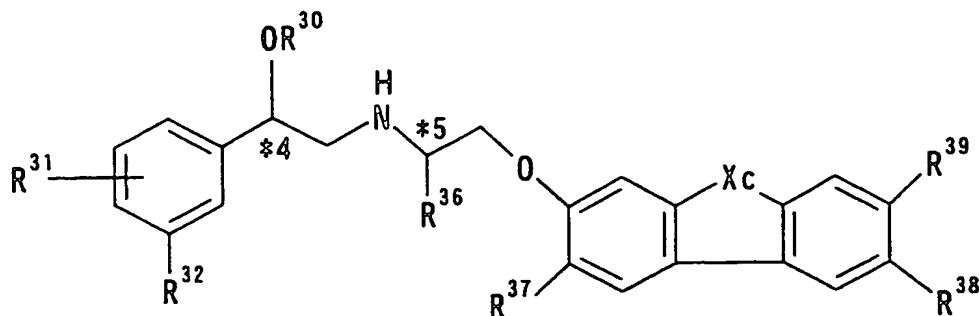
alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;  
 R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same meaning as above, or a salt thereof;

- 5 4) a compound of the formula [V] :



- wherein R<sup>20</sup> represents hydrogen atom or methyl group,  
 R<sup>21</sup> represents hydrogen atom, halogen atom, hydroxy group,  
 benzyloxy group, amino group or hydroxymethyl group,  
 10 R<sup>22</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>23</sup>,  
 SO<sub>2</sub>NR<sup>24</sup>R<sup>24'</sup> or nitro group,  
 R<sup>23</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>25</sup>, formyl  
 group or CONHR<sup>26</sup>,  
 R<sup>25</sup> represents a lower alkyl group, benzyl group or NR<sup>24</sup>R<sup>24'</sup>,  
 15 R<sup>24</sup> and R<sup>24'</sup> are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,  
 R<sup>26</sup> represents hydrogen atom or a lower alkyl group,  
 R<sup>26</sup> represents hydrogen atom or a lower alkyl group,  
 na is 1 or 2,  
 20 Xb represents secondary nitrogen atom, O or S,  
 one of R<sup>27</sup> or R<sup>28</sup> is hydrogen atom, and the other is hydrogen  
 atom, amino group, acetylamino group or hydroxy group, when  
 na is 1,  
 R<sup>28</sup> is hydrogen atom, and R<sup>27</sup> is hydrogen atom, amino group,  
 25 acetylamino group or hydroxy group, when na is 2,  
 \*1 represents an asymmetric carbon atom,  
 \*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and  
 R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof;  
 and  
 30 5) a compound of the formula [VI] :





wherein  $R^{30}$  represents hydrogen atom or methyl group,

$R^{21}$  represents hydrogen atom, a halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,

5  $R^{32}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  $SO_2NR^{34}R^{34'}$  or nitro group,

$R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl group or  $CONHR^{36'}$ ,

$R^{35}$  represents a lower alkyl group, benzyl group or  $NR^{34}R^{34'}$ ,

10  $R^{34}$  and  $R^{34'}$  are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

$R^{36'}$  represents hydrogen atom or a lower alkyl group,

$R^{36}$  represents hydrogen atom or a lower alkyl group,

15  $Xc$  represents secondary nitrogen atom, O, S or methylene group,

$R^{39}$  is hydrogen atom, one of  $R^{37}$  or  $R^{38}$  is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when  $Xc$  is secondary nitrogen atom, O or S,

20  $R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when  $Xc$  is methylene group,

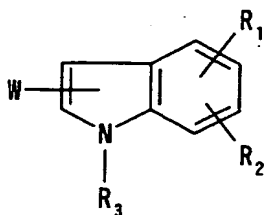
\*4 represents an asymmetric carbon atom,

25 \*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower alkyl group, or a salt thereof,

for the manufacture of a pharmaceutical preparation for treating diabetes, which is used in combination with an insulin sensitizer.

30 20. Use of an insulin sensitizer for the manufacture of

- a pharmaceutical preparation for treating impaired glucose tolerance, hyperlipidemia, hyperinsulinemia, obesity, hyperphagia, hypertension, cardiovascular diseases, polycystic ovary syndrome, gestational diabetes,
- 5 pancreatitis, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis, inflammatory bowel diseases, syndrome X, visceral fat obesity syndrome or diabetic complications, which is used in combination with at least one member selected from the group consisting of
- 10 1) a compound of the formula [I] :



- wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the
- 15 following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,
- 20 (a) a group of the formula :  $-Xa-Ra$   
 wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;
- (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$
- 25 wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,
- (c) a group of the formula :  $-O(CH_2)_r-Rc$
- 30 wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$

wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

(d) a group of the formula :  $-Y_a-(CH_2)_s-R_d$

wherein  $Y_a$  is NH or S,  $R_d$  is carboxyl group or a lower

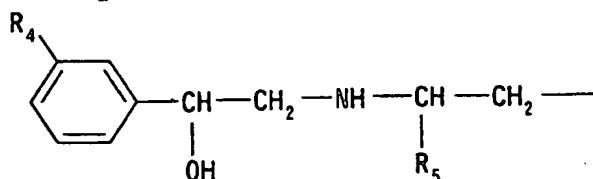
5 alkoxy carbonyl group,  $s$  is an integer of 1 to 4,

$R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above (b) or (c), or combines with  $R_1$  to form the above

10 methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

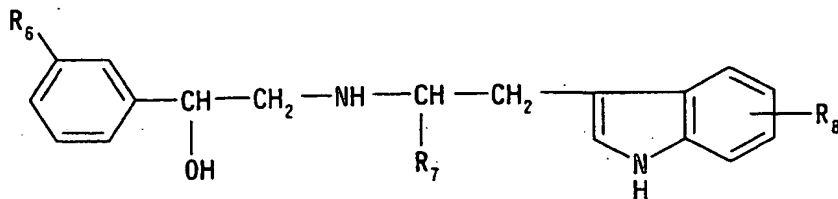
$R_3$  represents hydrogen atom or a lower alkyl group,

W represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;

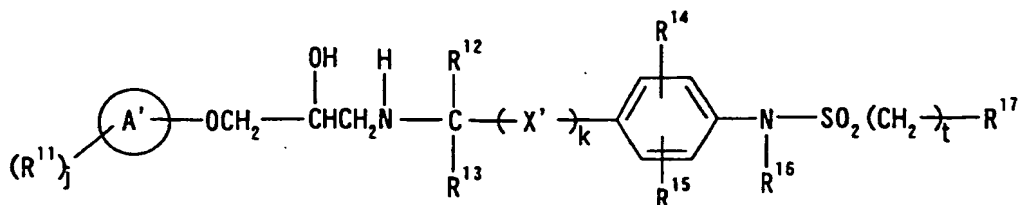
20 2) a compound of the formula [II] :



wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents

25 hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



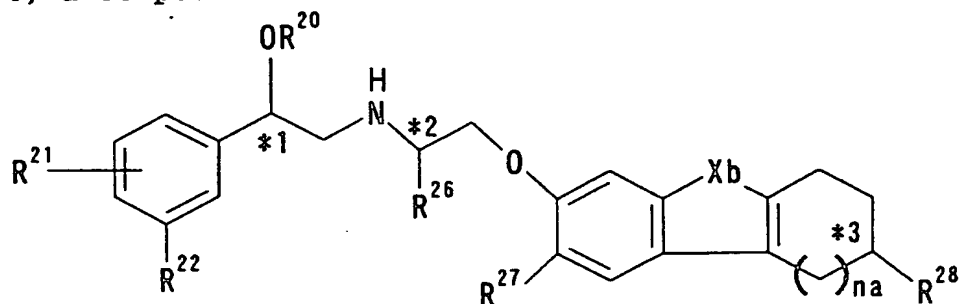
wherein j represents an integer of 0 to 7,

k represents 0 or 1,

t represents an integer of 0 to 3,

- 5 ring A' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms
- 10 selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 15 R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub>
- 20 alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;
- or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;
- R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl,
- 25 or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;
- X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;
- R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;
- R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;
- 30 R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub>, wherein R<sup>11</sup> and j have the same meanings as above;
- ring B' represents benzene ring; naphthalene ring; a 5- or

- 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 10 R<sup>18</sup> represents hydrogen atom; C<sub>1-10</sub> alkyl; C<sub>3-8</sub> cycloalkyl; phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; C<sub>1-10</sub> alkyl substituted by hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;
- 15 R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same meaning as above, or a salt thereof;
- 4) a compound of the formula [V] :



- wherein R<sup>20</sup> represents hydrogen atom or methyl group,
- 20 R<sup>21</sup> represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group, R<sup>22</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>23</sup>, SO<sub>2</sub>NR<sup>24</sup>R<sup>24'</sup> or nitro group,
- R<sup>23</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>25</sup>, formyl group or CONHR<sup>26</sup>,
- 25 R<sup>25</sup> represents a lower alkyl group, benzyl group or NR<sup>24</sup>R<sup>24'</sup>, R<sup>24</sup> and R<sup>24'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,
- R<sup>26</sup> represents hydrogen atom or a lower alkyl group,
- 30 R<sup>26</sup> represents hydrogen atom or a lower alkyl group,

na is 1 or 2,

Xb represents secondary nitrogen atom, O or S,  
one of R<sup>27</sup> or R<sup>28</sup> is hydrogen atom, and the other is hydrogen  
atom, amino group, acetylamino group or hydroxy group, when

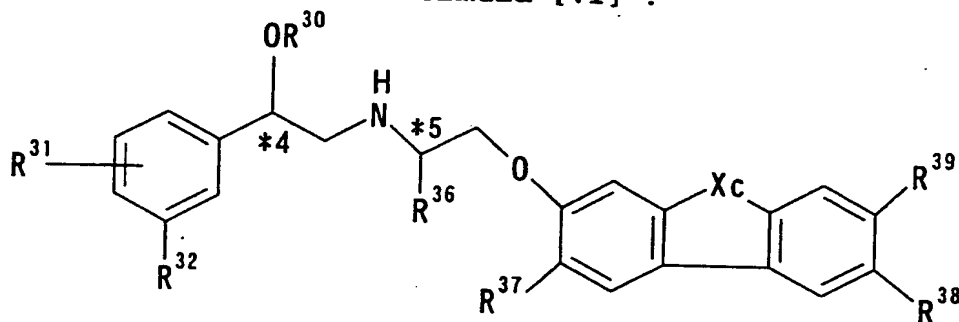
5 na is 1,

R<sup>28</sup> is hydrogen atom, and R<sup>27</sup> is hydrogen atom, amino group,  
acetylamino group or hydroxy group, when na is 2,

\*1 represents an asymmetric carbon atom,

\*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and  
10 R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof;  
and

5) a compound of the formula [VI] :



wherein R<sup>30</sup> represents hydrogen atom or methyl group,

15 R<sup>21</sup> represents hydrogen atom, a halogen atom, hydroxy group,  
benzyloxy group, amino group or hydroxymethyl group,

R<sup>32</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>33</sup>,  
SO<sub>2</sub>NR<sup>34</sup>R<sup>34'</sup> or nitro group,

R<sup>33</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>35</sup>, formyl  
20 group or CONHR<sup>36</sup>,

R<sup>35</sup> represents a lower alkyl group, benzyl group or NR<sup>34</sup>R<sup>34'</sup>,

R<sup>34</sup> and R<sup>34'</sup> are the same or different, and represent hydrogen  
atom, a lower alkyl group or benzyl group,

R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

25 R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

Xc represents secondary nitrogen atom, O, S or methylene  
group,

R<sup>39</sup> is hydrogen atom, one of R<sup>37</sup> or R<sup>38</sup> is hydrogen atom, and  
the other is hydrogen atom, amino group, acetylamino group  
30 or hydroxy group, when Xc is secondary nitrogen atom, O or

S,

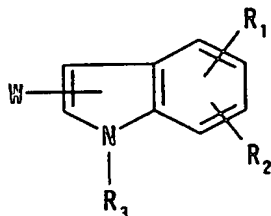
$R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is methylene group.

5 \*4 represents an asymmetric carbon atom,

\*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower alkyl group, or a salt thereof.

10 21. Use of at least one member selected from the group consisting of

1) a compound of the formula [I] :



wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

(a) a group of the formula :  $-Xa-Ra$

wherein Xa is O, S or NH, Ra is hydrogen atom or a lower alkyl group, provided that Ra is a lower alkyl group when Xa is S;

25 (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

wherein Rb is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group, Rbb is a lower alkoxy carbonyl group or carboxyl group, p is an integer of 0 to 3, q is 0 or 1,

30 (c) a group of the formula :  $-O(CH_2)_r-Rc$

wherein Rc is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl

group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$   
wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is  
an integer of 1 to 4,

(d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

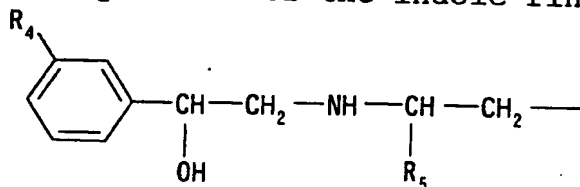
5 wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower  
alkoxycarbonyl group,  $s$  is an integer of 1 to 4,

$R_2$  represents hydrogen atom, a halogen atom, a lower alkyl  
group optionally substituted by hydroxyl group, hydroxyl  
group, a lower alkoxy group, or the same group as the above

10 (b) or (c), or combines with  $R_1$  to form the above  
methylenedioxy group, said methylenedioxy group being  
optionally substituted by carboxyl group or a lower  
alkoxycarbonyl group,

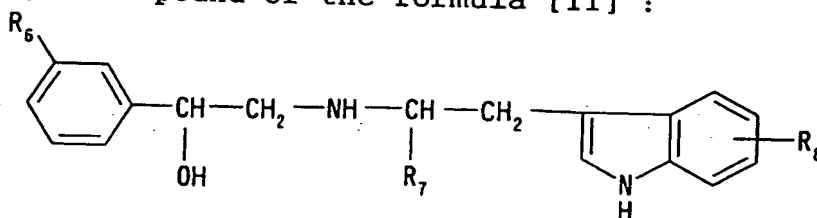
$R_3$  represents hydrogen atom or a lower alkyl group,

15 W represents a group of the formula which bonds to the 2-  
or 3-position of the indole ring in the formula [I]:



wherein  $R_4$  represents a halogen atom or a halogeno lower  
alkyl group,  $R_5$  represents a lower alkyl group, or a salt  
20 thereof;

2) a compound of the formula [II] :

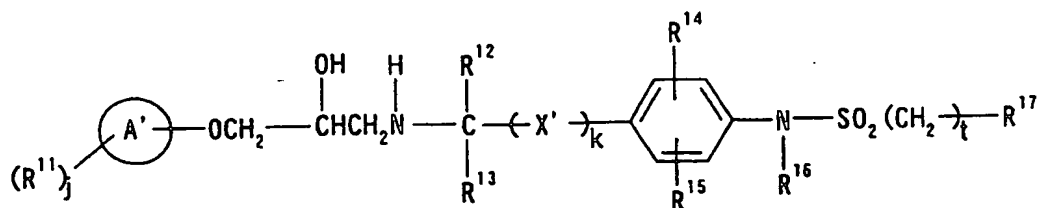


wherein  $R_6$  represents a halogen atom or a halogeno lower  
alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl  
25 group or a halogeno lower alkyl group,  $R_8$  represents  
hydrogen atom, a halogen atom, a halogeno lower alkyl group,  
nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



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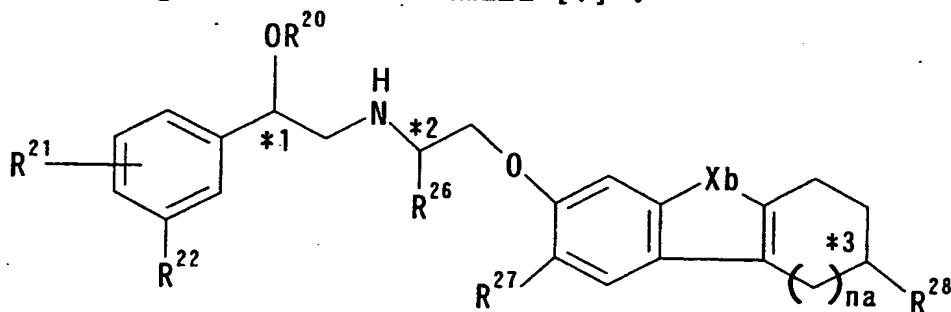
wherein j represents an integer of 0 to 7,

k represents 0 or 1,

t represents an integer of 0 to 3,

- 5 ring A' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms
- 10 selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 15 R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub>
- 20 alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;  
or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N;  
R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl,
- 25 or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;  
X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;  
R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;  
R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;
- 30 R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub>,  
wherein R<sup>11</sup> and j have the same meanings as above;  
ring B' represents benzene ring; naphthalene ring; a 5- or

- 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 10 R<sup>18</sup> represents hydrogen atom; C<sub>1-10</sub> alkyl; C<sub>3-8</sub> cycloalkyl; phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; C<sub>1-10</sub> alkyl substituted by hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;
- 15 R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same meaning as above, or a salt thereof;
- 4) a compound of the formula [V] :



- wherein R<sup>20</sup> represents hydrogen atom or methyl group,
- 20 R<sup>21</sup> represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,
- R<sup>22</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>23</sup>, SO<sub>2</sub>NR<sup>24</sup>R<sup>24'</sup> or nitro group,
- R<sup>23</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>25</sup>, formyl group or CONHR<sup>26'</sup>,
- 25 R<sup>25</sup> represents a lower alkyl group, benzyl group or NR<sup>24</sup>R<sup>24'</sup>,
- R<sup>24</sup> and R<sup>24'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,
- R<sup>26'</sup> represents hydrogen atom or a lower alkyl group,
- 30 R<sup>26</sup> represents hydrogen atom or a lower alkyl group,

na is 1 or 2,

Xb represents secondary nitrogen atom, O or S,

one of R<sup>27</sup> or R<sup>28</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when

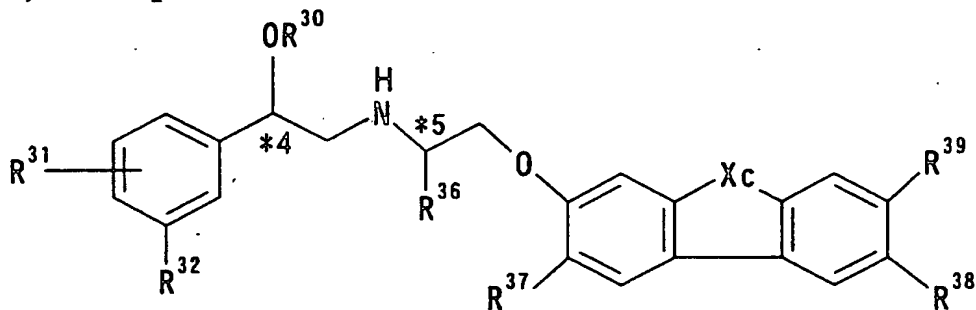
5 na is 1,

R<sup>28</sup> is hydrogen atom, and R<sup>27</sup> is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 2,

\*1 represents an asymmetric carbon atom,

10 \*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof; and

5) a compound of the formula [VI] :



wherein R<sup>30</sup> represents hydrogen atom or methyl group,

15 R<sup>21</sup> represents hydrogen atom, a halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group, R<sup>32</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>33</sup>, SO<sub>2</sub>NR<sup>34</sup>R<sup>34'</sup> or nitro group,

20 R<sup>33</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>35</sup>, formyl group or CONHR<sup>36</sup>,

R<sup>35</sup> represents a lower alkyl group, benzyl group or NR<sup>34</sup>R<sup>34'</sup>, R<sup>34</sup> and R<sup>34'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

25 R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

Xc represents secondary nitrogen atom, O, S or methylene group,

30 R<sup>39</sup> is hydrogen atom, one of R<sup>37</sup> or R<sup>38</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is secondary nitrogen atom, O or

S,

$R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is methylene group,

5 \*4 represents an asymmetric carbon atom,

\*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower alkyl group, or a salt thereof,

for the manufacture of a pharmaceutical preparation for treating impaired glucose tolerance, hyperlipidemia,

10 hyperinsulinemia, obesity, hyperphagia, hypertension, cardiovascular diseases, polycystic ovary syndrome,

gestational diabetes, pancreatitis, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis,

inflammatory bowel diseases, syndrome X, visceral fat

15 obesity syndrome or diabetic complications;

which is used in combination with an insulin sensitizer.

22. Use according to claim 20 or 21, wherein the diabetic complications are retinopathy, nephropathy, neuropathy,

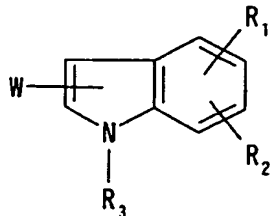
20 macroangiopathy, diabetic hyperosmolar coma, infectious disease, diabetic osteoporosis, diabetic gangrene,

xerostomia, lowered sense of hearing, myocardial infarction, angina pectoris, cerebrovascular disease or peripheral circulatory disturbance.

25

23. Use of at least one member selected from the group consisting of

1) a compound of the formula [I] :



30 wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower

alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower

5 alkoxy carbonyl group,

(a) a group of the formula :  $-Xa-Ra$

wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;

10 (b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,

15 (c) a group of the formula :  $-O(CH_2)_r-Rc$

wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$  wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

20

(d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,

$R_2$  represents hydrogen atom, a halogen atom, a lower alkyl

25 group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above

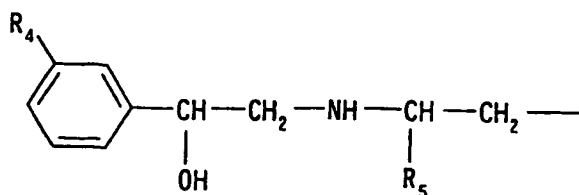
(b) or (c), or combines with  $R_1$  to form the above

methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower

30 alkoxy carbonyl group,

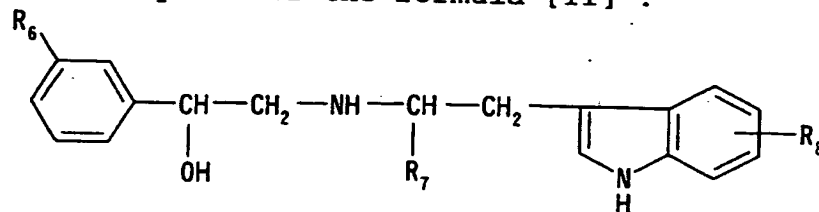
$R_3$  represents hydrogen atom or a lower alkyl group,

$W$  represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



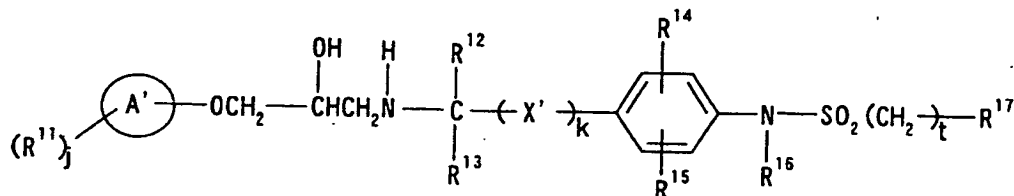
wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;

- 5 2) a compound of the formula [II] :



wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

- 10 3) a compound of the formula [III] :



wherein  $j$  represents an integer of 0 to 7,  
 15  $k$  represents 0 or 1,  
 $t$  represents an integer of 0 to 3,  
 ring  $A'$  represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with  $C_{3-8}$   
 20 cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic  
 25 ring containing 1 to 3 hetero atoms selected from O, S and

N;

R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>,

- 5 NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;

- or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group  
10 containing 1 to 3 hetero atoms selected from O, S and N;  
R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;  
X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;

- R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl,  
15 halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;

R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;

R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>)<sub>j</sub>,

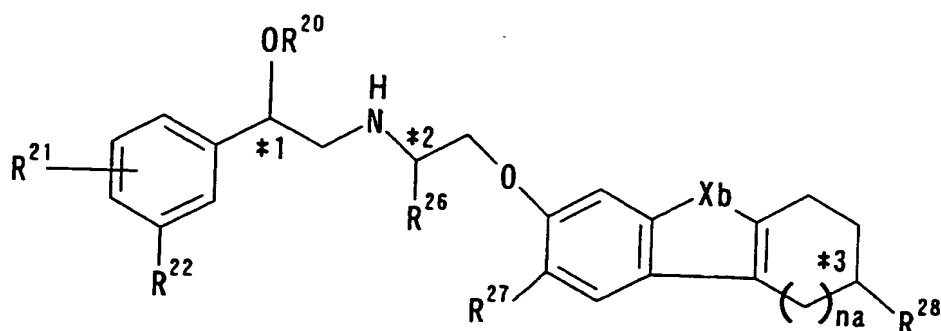
wherein R<sup>11</sup> and j have the same meanings as above;

- ring B' represents benzene ring; naphthalene ring; a 5- or  
20 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic  
25 ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;  
N;

- R<sup>18</sup> represents hydrogen atom; C<sub>1-10</sub> alkyl; C<sub>3-8</sub> cycloalkyl;  
30 phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; C<sub>1-10</sub> alkyl substituted by hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

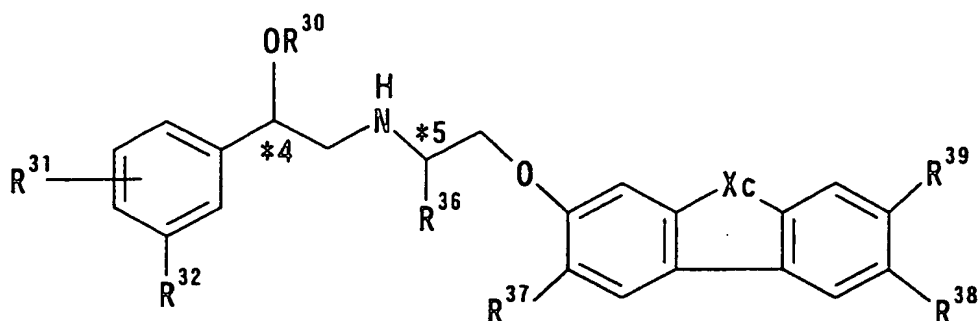
- R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same  
35 meaning as above, or a salt thereof;

4) a compound of the formula [V] :



- wherein  $R^{20}$  represents hydrogen atom or methyl group,  
 $R^{21}$  represents hydrogen atom, halogen atom, hydroxy group,  
 benzyloxy group, amino group or hydroxymethyl group,  
 5  $R^{22}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{23}$ ,  
 $SO_2NR^{24}R^{24'}$  or nitro group,  
 $R^{23}$  represents hydrogen atom, methyl group,  $SO_2NR^{25}$ , formyl  
 group or  $CONHR^{26'}$ ,  
 $R^{25}$  represents a lower alkyl group, benzyl group or  $NR^{24}R^{24'}$ ,  
 10  $R^{24}$  and  $R^{24'}$  are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,  
 $R^{26'}$  represents hydrogen atom or a lower alkyl group,  
 $R^{26}$  represents hydrogen atom or a lower alkyl group,  
 $na$  is 1 or 2,  
 15  $Xb$  represents secondary nitrogen atom, O or S,  
 one of  $R^{27}$  or  $R^{28}$  is hydrogen atom, and the other is hydrogen  
 atom, amino group, acetylamino group or hydroxy group, when  
 $na$  is 1,  
 $R^{28}$  is hydrogen atom, and  $R^{27}$  is hydrogen atom, amino group,  
 20 acetylamino group or hydroxy group, when  $na$  is 2,  
 $*1$  represents an asymmetric carbon atom,  
 $*2$  and  $*3$  represent an asymmetric carbon atom when  $R^{26}$  and  
 $R^{28}$  are respectively not hydrogen atom, or a salt thereof;  
 and  
 25 5) a compound of the formula [VI] :





wherein  $R^{30}$  represents hydrogen atom or methyl group,  
 $R^{21}$  represents hydrogen atom, a halogen atom, hydroxy group,  
 benzyloxy group, amino group or hydroxymethyl group,  
 5  $R^{22}$  represents hydrogen atom, hydroxymethyl group,  $NHR^{33}$ ,  
 $SO_2NR^{34}R^{34'}$  or nitro group,

$R^{33}$  represents hydrogen atom, methyl group,  $SO_2NR^{35}$ , formyl  
 group or  $CONHR^{36}$ ,

$R^{35}$  represents a lower alkyl group, benzyl group or  $NR^{34}R^{34'}$ ,

10  $R^{34}$  and  $R^{34'}$  are the same or different, and represent hydrogen  
 atom, a lower alkyl group or benzyl group,

$R^{36}$  represents hydrogen atom or a lower alkyl group,

$R^{36}$  represents hydrogen atom or a lower alkyl group,

15  $Xc$  represents secondary nitrogen atom, O, S or methylene  
 group,

$R^{39}$  is hydrogen atom, one of  $R^{37}$  or  $R^{38}$  is hydrogen atom, and  
 the other is hydrogen atom, amino group, acetylamino group  
 or hydroxy group, when  $Xc$  is secondary nitrogen atom, O or  
 S,

20  $R^{37}$  and  $R^{38}$  are both hydrogen atom, and  $R^{39}$  is hydrogen atom,  
 amino group, acetylamino group or hydroxy group, when  $Xc$   
 is methylene group,

\*4 represents an asymmetric carbon atom,

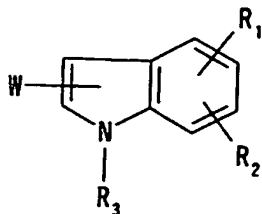
25 \*5 represents an asymmetric carbon atom when  $R^{36}$  is a lower  
 alkyl group, or a salt thereof,

for the manufacture of a pharmaceutical preparation for  
 inhibiting body weight increase after stopping a smoking  
 habit.

30 24. Use of at least one member selected from the group

consisting of

1) a compound of the formula [I] :



wherein  $R_1$  represents a lower alkyl group optionally substituted by hydroxyl group, phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with  $R_2$  to form methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

(a) a group of the formula :  $-Xa-Ra$

wherein  $Xa$  is O, S or NH,  $Ra$  is hydrogen atom or a lower alkyl group, provided that  $Ra$  is a lower alkyl group when  $Xa$  is S;

(b) a group of the formula :  $-[O(CH_2)_p-CH(Rb)]_qRbb$

wherein  $Rb$  is hydrogen atom, a lower alkyl group, a lower alkoxy carbonyl group or carboxyl group,  $Rbb$  is a lower alkoxy carbonyl group or carboxyl group,  $p$  is an integer of 0 to 3,  $q$  is 0 or 1,

(c) a group of the formula :  $-O(CH_2)_r-Rc$

wherein  $Rc$  is a lower alkanoyl group, hydroxyl group, cyano group, phenyl group, a mono- or di-lower alkylaminocarbonyl group or a group of the formula :  $-P(=O)(OR_A)(OR_A)$

wherein  $R_A$  is hydrogen atom or a lower alkyl group,  $r$  is an integer of 1 to 4,

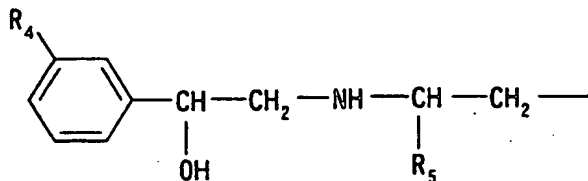
(d) a group of the formula :  $-Ya-(CH_2)_s-Rd$

wherein  $Ya$  is NH or S,  $Rd$  is carboxyl group or a lower alkoxy carbonyl group,  $s$  is an integer of 1 to 4,

$R_2$  represents hydrogen atom, a halogen atom, a lower alkyl group optionally substituted by hydroxyl group, hydroxyl group, a lower alkoxy group, or the same group as the above

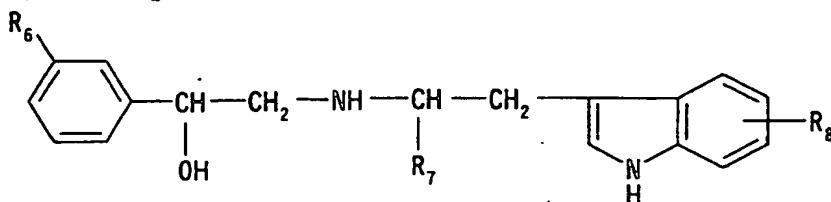
(b) or (c), or combines with  $R_1$  to form the above methylenedioxy group, said methylenedioxy group being optionally substituted by carboxyl group or a lower alkoxy carbonyl group,

- 5  $R_2$  represents hydrogen atom or a lower alkyl group,  
 $W$  represents a group of the formula which bonds to the 2- or 3-position of the indole ring in the formula [I]:



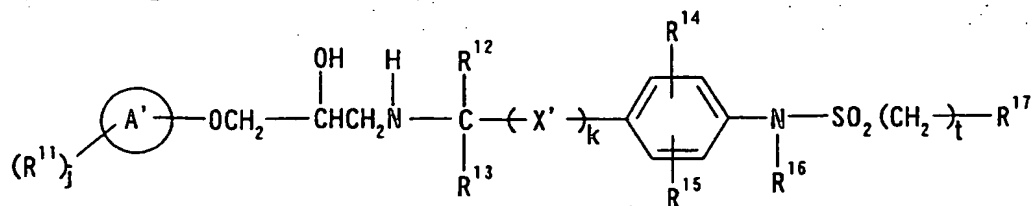
- wherein  $R_4$  represents a halogen atom or a halogeno lower alkyl group,  $R_5$  represents a lower alkyl group, or a salt thereof;

2) a compound of the formula [II] :



- wherein  $R_6$  represents a halogen atom or a halogeno lower alkyl group,  $R_7$  represents hydrogen atom, a lower alkyl group or a halogeno lower alkyl group,  $R_8$  represents hydrogen atom, a halogen atom, a halogeno lower alkyl group, nitro group or cyano group, or a salt thereof;

3) a compound of the formula [III] :



20

wherein  $j$  represents an integer of 0 to 7,

$k$  represents 0 or 1,

$t$  represents an integer of 0 to 3,

ring  $A'$  represents benzene ring; naphthalene ring; a 5- or

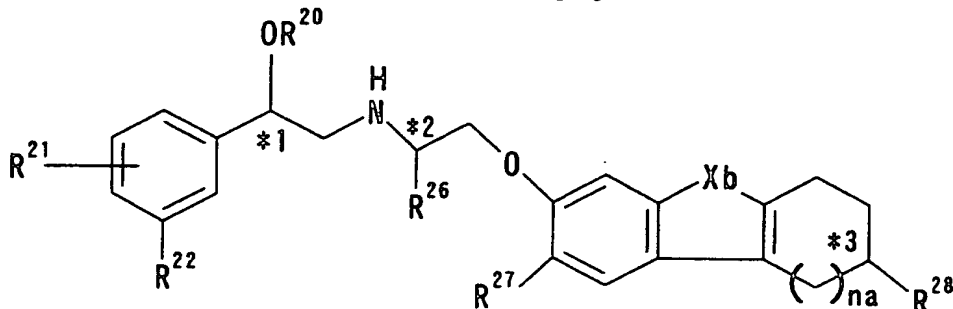
25 6-membered heterocyclic ring containing 1 to 4 hetero atoms

- selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N;
- 5 R<sup>11</sup> represents hydroxy, oxo, halogen, cyano, nitro, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>; or a C<sub>1-6</sub> alkyl group substituted by hydroxy, nitro, halogen, cyano, NR<sup>18</sup>R<sup>18</sup>, SR<sup>18</sup>, a halogeno lower alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, NR<sup>18</sup>COR<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, NR<sup>18</sup>SO<sub>2</sub>R<sup>19</sup> or NR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>;
- 10 or R<sup>11</sup> represents a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from O, S and N; R<sup>12</sup> and R<sup>13</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted by hydroxy, C<sub>1-6</sub> alkoxy or halogen;
- 15 X' represents -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>O-;
- 20 R<sup>14</sup> and R<sup>15</sup> represent independently hydrogen atom, C<sub>1-6</sub> alkyl, halogen, NHR<sup>18</sup>, OR<sup>18</sup>, SO<sub>2</sub>R<sup>19</sup> or NHSO<sub>2</sub>R<sup>19</sup>;
- R<sup>16</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl;
- R<sup>17</sup> represents C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl or -B'-(R<sup>11</sup>),
- 25 wherein R<sup>11</sup> and j have the same meanings as above; ring B' represents benzene ring; naphthalene ring; a 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from O, S and N; benzene ring condensed with C<sub>3-8</sub> cycloalkyl ring; benzene ring condensed with a 5- or 6-
- 30 membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N; or a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and N which is condensed with a 5- or 6-membered heterocyclic ring containing 1 to 3 hetero atoms selected from O, S and
- 35 N;
- R<sup>18</sup> represents hydrogen atom; C<sub>1-10</sub> alkyl; C<sub>3-8</sub> cycloalkyl;

phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; C<sub>1-10</sub> alkyl substituted by hydroxy, halogen, CO<sub>2</sub>H, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, or phenyl substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

- 5 R<sup>19</sup> represents R<sup>18</sup>, NHR<sup>18</sup> or NR<sup>18</sup> wherein R<sup>18</sup> has the same meaning as above, or a salt thereof;

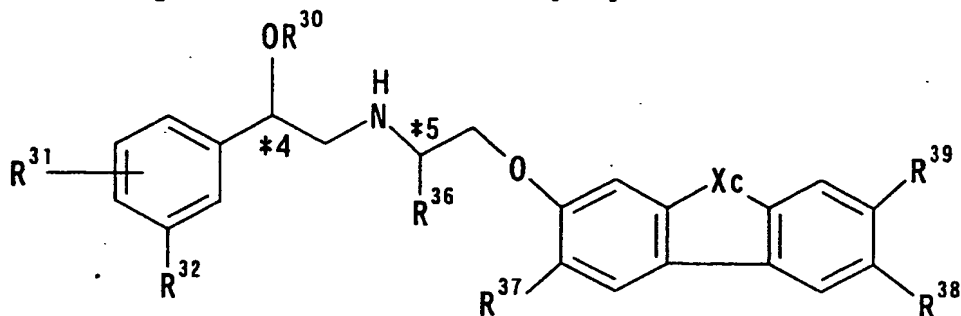
4) a compound of the formula [V] :



- wherein R<sup>20</sup> represents hydrogen atom or methyl group,
- 10 R<sup>21</sup> represents hydrogen atom, halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group, R<sup>22</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>23</sup>, SO<sub>2</sub>NR<sup>24</sup>R<sup>24'</sup> or nitro group, R<sup>23</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>25</sup>, formyl
- 15 group or CONHR<sup>26'</sup>, R<sup>25</sup> represents a lower alkyl group, benzyl group or NR<sup>24</sup>R<sup>24'</sup>, R<sup>24</sup> and R<sup>24'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group, R<sup>26'</sup> represents hydrogen atom or a lower alkyl group,
- 20 R<sup>26</sup> represents hydrogen atom or a lower alkyl group, na is 1 or 2, Xb represents secondary nitrogen atom, O or S, one of R<sup>27</sup> or R<sup>28</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when
- 25 na is 1, R<sup>28</sup> is hydrogen atom, and R<sup>27</sup> is hydrogen atom, amino group, acetylamino group or hydroxy group, when na is 2, \*1 represents an asymmetric carbon atom, \*2 and \*3 represent an asymmetric carbon atom when R<sup>26</sup> and
- 30 R<sup>28</sup> are respectively not hydrogen atom, or a salt thereof;

and

5) a compound of the formula [VI] :



wherein R<sup>30</sup> represents hydrogen atom or methyl group,

5 R<sup>21</sup> represents hydrogen atom, a halogen atom, hydroxy group, benzyloxy group, amino group or hydroxymethyl group,

R<sup>32</sup> represents hydrogen atom, hydroxymethyl group, NHR<sup>33</sup>, SO<sub>2</sub>NR<sup>34</sup>R<sup>34'</sup> or nitro group,

10 R<sup>33</sup> represents hydrogen atom, methyl group, SO<sub>2</sub>NR<sup>35</sup>, formyl group or CONHR<sup>36'</sup>,

R<sup>35</sup> represents a lower alkyl group, benzyl group or NR<sup>34</sup>R<sup>34'</sup>,

R<sup>34</sup> and R<sup>34'</sup> are the same or different, and represent hydrogen atom, a lower alkyl group or benzyl group,

R<sup>36'</sup> represents hydrogen atom or a lower alkyl group,

15 R<sup>36</sup> represents hydrogen atom or a lower alkyl group,

Xc represents secondary nitrogen atom, O, S or methylene group,

20 R<sup>39</sup> is hydrogen atom, one of R<sup>37</sup> or R<sup>38</sup> is hydrogen atom, and the other is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is secondary nitrogen atom, O or S,

R<sup>37</sup> and R<sup>38</sup> are both hydrogen atom, and R<sup>39</sup> is hydrogen atom, amino group, acetylamino group or hydroxy group, when Xc is methylene group,

25 \*4 represents an asymmetric carbon atom,

\*5 represents an asymmetric carbon atom when R<sup>36</sup> is a lower alkyl group, or a salt thereof,

30 for the manufacture of a pharmaceutical preparation for inhibiting body weight increase after stopping alimentary therapy.